THE FORMATION AND REACTIVITY OF PHOSPHORUS-CARBON SYSTEMS

by

B.D. PLACE

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for the degree of

DOCTOR OF PHILOSOPHY

PREFACE

The work described in this dissertation was carried out in the School of Molecular Sciences, University of Warwick, Coventry, between October, 1966 and July, 1969. It is the original work of the author, except where specific acknowledgement is made, and has not been submitted for a degree at any other University.

The author wishes to express his thanks to Professor V. M. Clark, who directed this work, and to Dr. D. W. Hutchinson for their unstinting interest, advice and encouragement.

The award of a Research Studentship by the Science Research Council is gratefully acknowledged.

CONTENTS

SUMMARY

In this thesis the *in vivo* cleavage of the phosphorus-carbon bond of 2-aminoethyl phosphonic acid (AEP) is discussed, and attempts to achieve a similar cleavage *in vitro* investigated. Diazotisation of AEP failed to cause P-C bond rupture but led instead to 2-hydroxyethyl phosphonic acid, which itself was unexpectedly labile, undergoing fragmentation to ethylene and inorganic phosphate. A mechanism involving a 4-membered phosphorus containing ring is proposed to explain this lability. An improved synthetic route to amino-phosphonic acids has been developed and is discussed.

The rearrangement of phosphoenol pyruvate to 3-phosphono pyruvate as a step in the biosynthesis of AEP has been studied in the general context of 4-centre rearrangements. The evidence for these rearrangements in phosphorus chemistry, together with analogous observations in carbon chemistry, is reviewed and discussed. Evidence for the rearrangement of enol phosphates to β-keto phosphonates, although in very low yields, is presented and the significance of this observation discussed.

The relationship between enol phosphates and β-keto-phosphonates in the Perkow reaction has stimulated some work directed towards an understanding of the mechanism of the reaction. Whilst the results of experiments with acyclic phosphates and halocarbonyl compounds can be adequately explained by existing theories of the Perkow reaction mechanism, other studies have necessitated a reappraisal of the route to enol phosphates in certain cases.

Chloral was found to react with cyclic phosphates to form relatively stable intermediates. These intermediates were characterised and shown to contain pentacovalent phosphorus. Thermal decomposition has been shown to yield enol phosphates. On the basis of these results, a mechanism has been proposed for the course of the reaction between cyclic phosphites and α-halocarbonyl compounds. Scanty evidence has been obtained for similar intermediates in "normal" Perkow reactions.

A parallel has been drawn between the Perkow reaction and the reaction of other activated carbonyl compounds with phosphites.

Ohne Phosphor kein Gedanke

Jacob Moleschott

Lehre der Nahrungsmittel, ii, 1, 4

INTRODUCTION

INTRODUCTION

AMINOPHOSPHONIC ACIDS

Natural occurrence:

In view of the stability of the phosphorus-carbon bond in aminophosphonic acids, Chavane[1], in 1947, commented on the possibility that such acids, analogous to the widely distributed aminocarboxylic acids, could exist in nature. It was not until 1959 that this prediction was verified by the reports[2,3] of the isolation of an aminophosphonic acid from a "proteolipid-like" extract of sheep rumen protozoa. Subsequently, isolation of the same amino-acid, 2-aminoethyl phosphonic acid (AEP, I), from the sea anemone Anthopleura Elegantissima was reported[2].

Following these early reports, considerable activity developed in the field of aminophosphonic acid chemistry and biochemistry; chiefly the latter. Apart from efforts directed towards the synthesis of aminophosphonic acids and their derivatives[4-6], several laboratories undertook studies aimed at the elucidation of the distribution, biosynthesis and metabolism of AEP (and subsequently, of related amino-phosphonic acids).

The aminophosphonic acids appear to be fairly widespread in nature, particularly AEP itself, which has been isolated from protozoa[2,3,7-9], various coelenterates[9-14], molluscs[12,13,15] starfish[12,13] and even mammalian tissues such as liver and brain[16-18]. The N-methylated derivatives of AEP have all been isolated from the sea anemone Anthopleura Xanthogrammica[6]. AEP has been found as a component of phospholipids[2,3,10]. Baer[19] has pioneered the synthesis

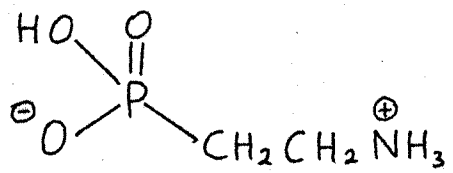
of phosphonic acid analogues of phospholipids ("phosphonolipids") and concomitant with this work the isolation and identification of naturally occurring phosphonolipids was reported from several laboratories.[14,20-27]

In addition, 72 per cent of the AEP present in the sea anemone Metridium Dianthus was in the lipid-free, insoluble residue, presumably bound to proteins[12]. Dinitrophenylation studies indicated that the amino-group of AEP was blocked, suggesting that this group was involved in a peptide linkage. Very recently[28], workers at the University of British Columbia have isolated pure proteins containing several residues of AEP (Proteases A and B, from the sea anemone Metridium Senile).

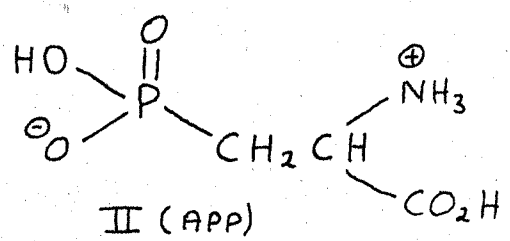
Furthermore, in the sea anemone Anthopleura Xanthogrammica, N-methyl AEP (78 per cent) and AEP (22 per cent) both occur bound to proteins[29].

Biosynthesis

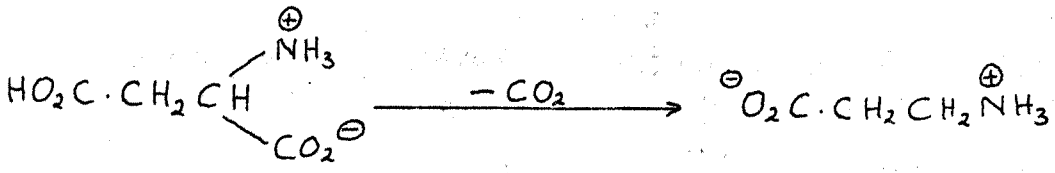
Kittredge[9], postulating an analogy of biosynthetic pathways between aminocarboxylic acids and aminophosphonic acids (Figure I), sought and found 2-amino-3-phosphono propionic acid (APP, II), the carboxylated precursor of AEP (Table I). By further analogy with the sulphonic acid analogues of AEP and APP, taurine (III) and cysteic acid (IV) respectively, it was considered[19,30] possible that "reduced forms of phosphorus" might be involved in the biosynthetic route. An extensive search for such reduced forms of phosphorus proved fruitless.



I (AEP)

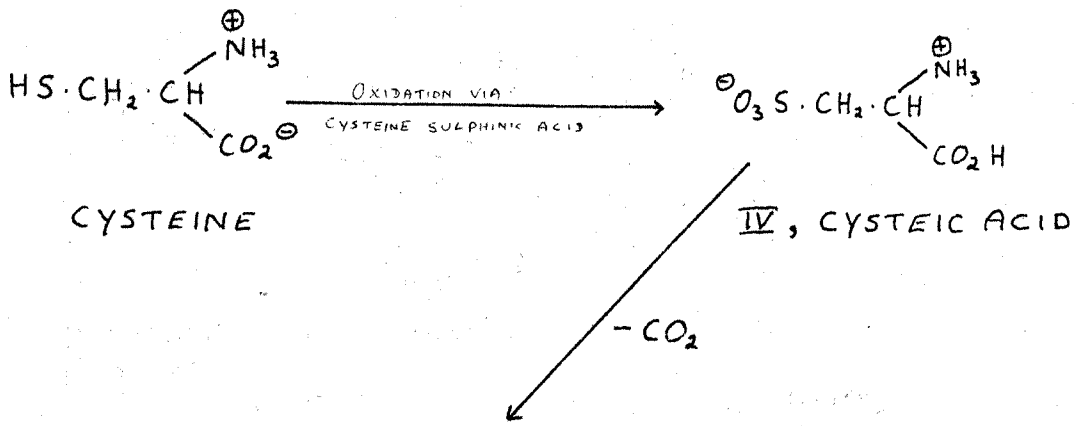


II (APP)



ASPARTIC ACID

β-ALANINE



CYSTEINE

OXIDATION VIA CYSTEINE SULPHINIC ACID

IV, CYSTEIC ACID

TAURINE

III, TAURINE

FIGURE I BIOSYNTHESIS OF TAURINE, CYSTEIC ACID AND β-ALANINE

TABLE I

Relationships between phosphonic, phosphoric and carboxylic amino-acids[19]

R	Phosphonic acid	Phosphoric acid	Carboxylic acid
	$R.PO_3H_2$	$RO-PO_3H_2$	$R.CO_2H$
$H_2NCH_2CH_2-$	AEP	Ethanolamine phosphate	β-alanine
$CH_3NH.CH_2CH_2-$	N-methyl AEP	N-methyl ethanolamine phosphate	N-methyl-β-alanine
$(CH_3)_3\overset{+}{N}.CH_2CH_2-$	N,N,N-trimethyl AEP	Choline phosphate	N,N,N-trimethyl β-alanine
HO_2C | $H_2N-CH.CH_2-$	APP	Serine phosphate	Aspartic acid

Meanwhile, Segal[31] had proposed a biosynthetic scheme for APP and AEP involving a phosphoramidic acid rearrangement (Figure II).

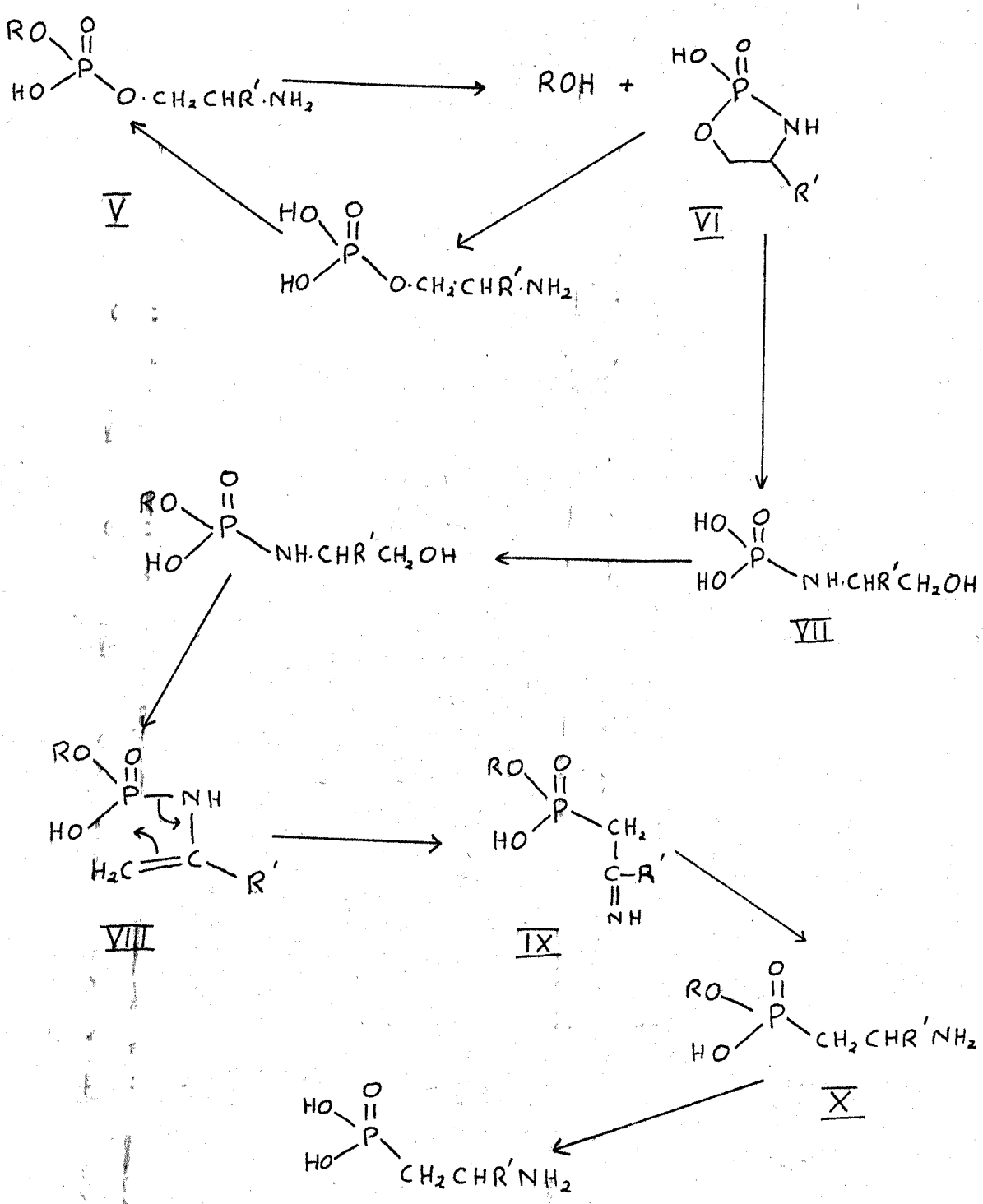
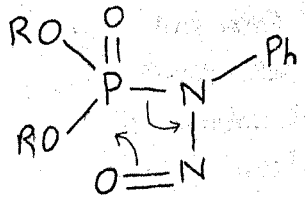
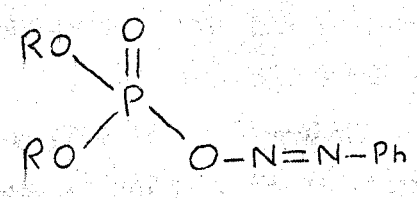


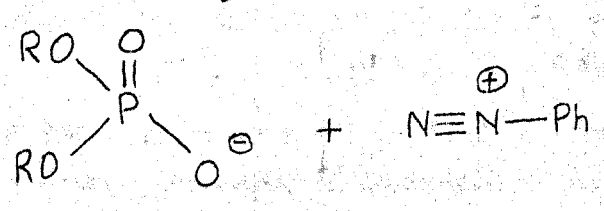
FIGURE II SEGAL SCHEME FOR BIOSYNTHESIS OF AEP AND APP



XI



XII

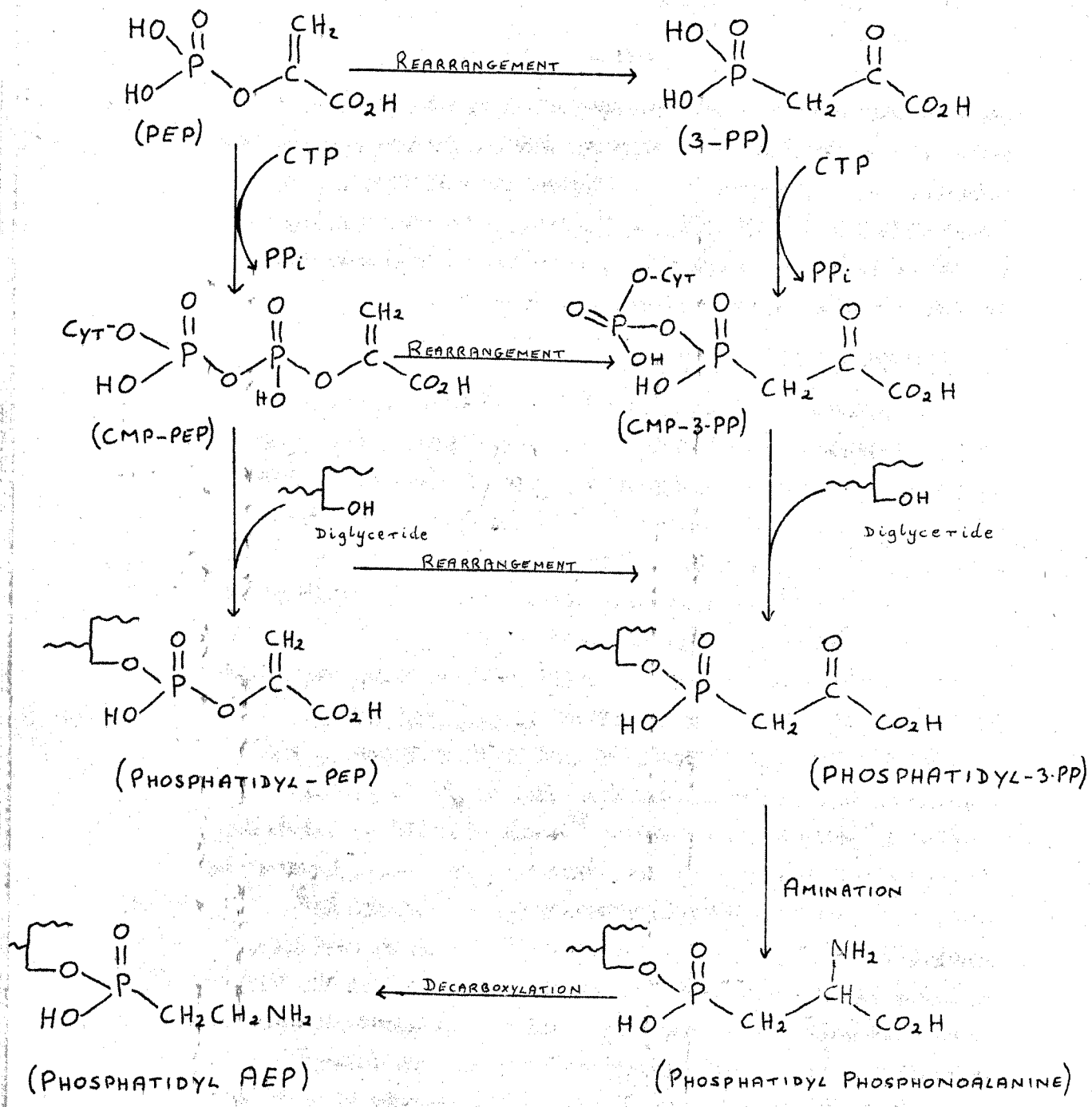


Analogies for the various steps of the Segal scheme are well established. Thus phosphatidyl ethanolamine or phosphatidyl serine (V,R=H or CO_2H) represents the amino analogue of a glyceryl monophosphate ester, several examples of which are known to transfer phosphate[32-36] from one oxygen to another (e.g. in the formation and subsequent cleavage of cyclic phosphates). In the Segal scheme, the cyclic ester-amide (VI) can cleave to produce the O- or N-phosphoryl ethanolamine or serine (VII,R=H or CO_2H), the latter being employed in the elaboration of AEP or APP, the former becoming available for re-esterification. Phosphorus-nitrogen bonded species are known to exist in nature, e.g. N-phosphoro creatine and N-phosphoro arginine. It should be pointed out, however, that these are phosphoroguanidates and not the more labile phosphoramidates.

Dehydration of (VII) to (VIII) is analogous to the enolase-catalysed dehydration of phosphoglyceric acid to phosphoenol pyruvate[37]. Direct analogy for the rearrangement of the N-vinyl phosphoramidate (VIII) to the imine (IX) has not been observed, though the rearrangement of an N-nitroso phosphoramidate to the corresponding "diazo-phosphate" (XI $\longrightarrow$ XII)[38] is probably related.

Reduction of the imine (IX) to the phosphonolipid (X) presumably occurs with the aid of NADH. Hydrolysis of (X) would lead to (I) or (II).

It should be pointed out that the Segal scheme is unsupported by experimental evidence. On the other hand, four independent groups have subsequently reported[30,39-41]



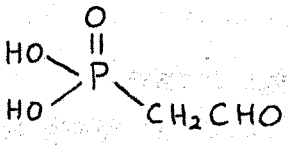
PEP: Phosphoenol pyruvate
3-PP: 3-phosphonopyruvate
CTP: Cytidine triphosphate
CMP-PEP: Cytidine monophosphate-PEP
PPi: Inorganic pyrophosphate

FIGURE III[19]

experimental evidence that phosphoenol pyruvate (PEP) is a precursor of APP (and subsequently, AEP). The scheme for the biosynthesis of AEP from PEP, obtained by a combination of those advanced (Figure III), suggests a 4-centre rearrangement of PEP at an undetermined stage, followed by transamination to give APP and decarboxylation of APP to AEP.

Metabolism and catabolism

The metabolic function of AEP and related compounds remains obscure, though evidence to date suggests that aminophosphonates act as a "reserve store" of phosphorus. This view was particularly strengthened by the observation that several species of bacteria, for example, were able to metabolise aminophosphonic acids and return the phosphorus to the circulating pool as inorganic phosphate (P_i) [42-44]. AEP was shown to be the most readily utilised phosphonic acid in this system[45]. A mutant strain of Bacillus Cereus, capable of using AEP as its sole source of phosphorus, was studied in an attempt to elucidate the catabolic pathway leading to phosphate[46]. Using ^{32}P-labelled AEP as substrate, a radioactive intermediate was observed which was subsequently shown [47,48] to be 2-phosphonoacetaldehyde. Chavane had predicted[49] that 2-phosphonoacetaldehyde would be unstable. He based his prediction on the relationship between the "polarity" of substituents on the alkyl side chain of phosphonates and the stability of the phosphorus-carbon bond[47]. De Koning[50], in his studies of the reaction of AEP with ninhydrin (Figure IV), had shown that complete fragmentation of AEP to acetaldehyde and phosphate occurred at pH5 when heated to 96°C for 8 hours.



XIII

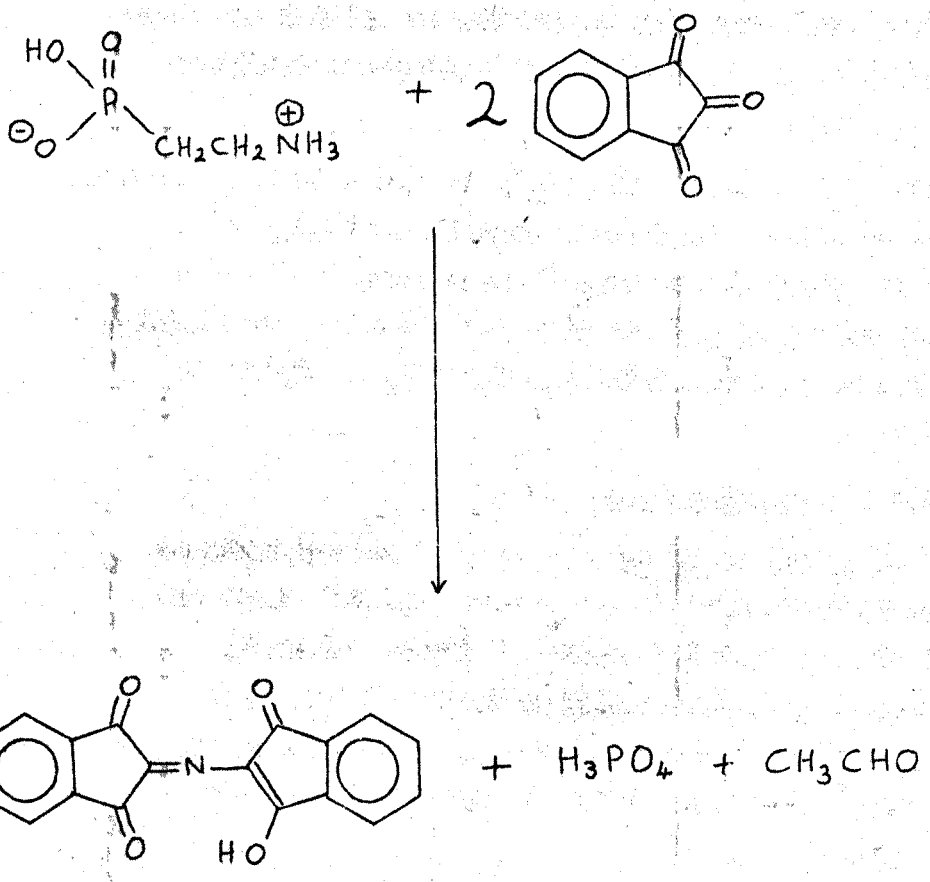


FIGURE IV

Such instability was remarkable when compared with the stability of AEP in strong acid (6-10N) in which it could be refluxed for 48 hours without change. α-aminophosphonic acids have been shown[51] to generate metaphosphate on reaction with ninhydrin.

In view of the rationale proposed[52] for P-XYZ activation leading to phosphoryl transfer, especially as related to β-keto-alkyl phosphonates, the instability of 2-phosphonoacetaldehyde becomes less surprising.

The successful synthesis of (XIII) enabled a test of Chavane's prediction to be made. Complete conversion of (XIII) to acetaldehyde and phosphate occurred[47] on heating in aqueous sodium acetate buffer at pH5 and 90°C for 8 hours. Conversely, at low and high pH values, (XIII) was found to be stable in aqueous solutions.

Synthesis of aminophosphonic acids

Methods of synthesis of AEP and related aminophosphonic acids, though well-known[1,53,54], suffered uniformly from the disadvantage of producing low yields of impure material. A simple, high-yield procedure was thus developed (see next section), the outline of which had been suggested at an American Chemical Society meeting by Isbell[55]; details have yet to be published. (Figure V).

ENOL PHOSPHATE REARRANGEMENTS

The early postulate, by Segal, of a phosphoramidic acid rearrangement as a biosynthetic route to AEP is of more general interest, as is the subsequent suggestion of a phosphoenol

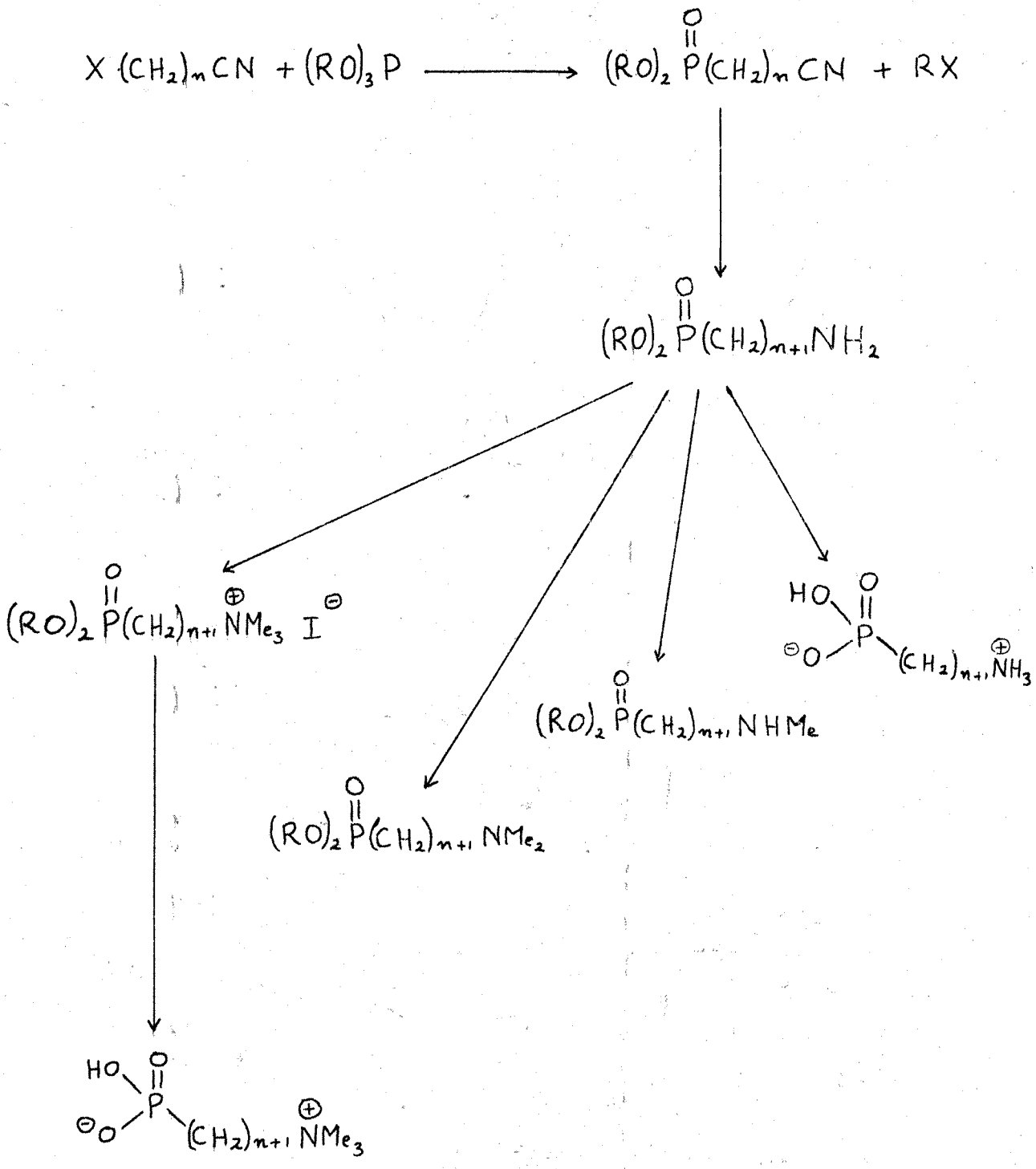
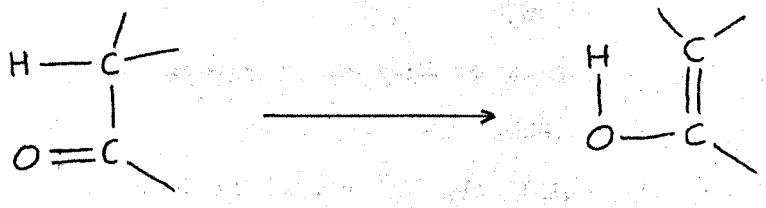
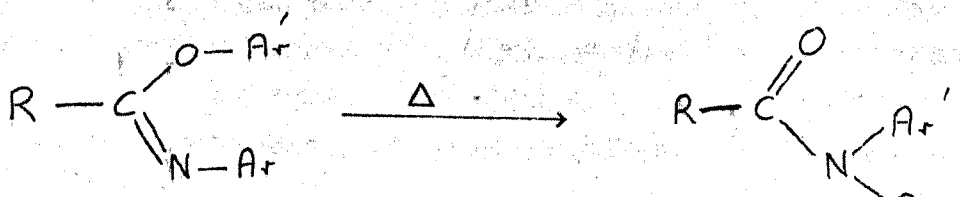

X(CH2)nCN + (RO)3P
(RO)2P(CH2)nCN + RX
(RO)2P(CH2)n+1NH2
(RO)2P(CH2)n+1NMe3 I⊖
(RO)2P(CH2)n+1NHMe
(RO)2P(CH2)n+1NMe2
HO
⊖O
(CH2)n+1⊕NH3
HO
⊖O
(CH2)n+1⊕NMe3

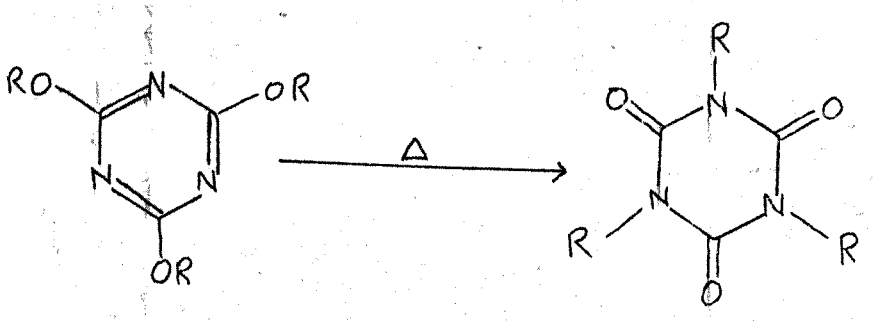
FIGURE V



XIV XV



XVI XVII

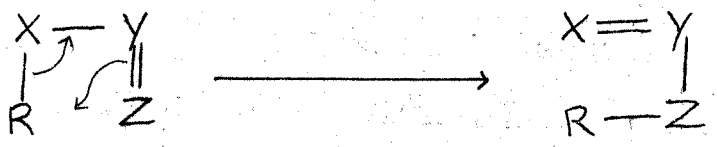


O-ALKYL CYANURATE N-ALKYL ISOCYANURATE

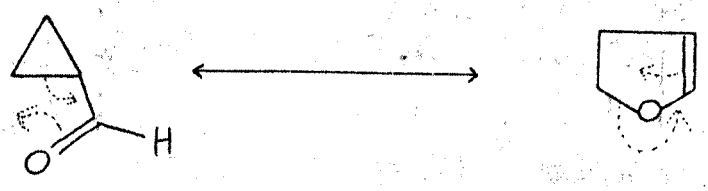
pyruvate rearrangement, in that it represents a group of 4-centre rearrangements in phosphorus chemistry.

Four-centre rearrangements are well-known in carbon chemistry. Perhaps the simplest case is that of 1,3-prototropy which can be envisaged either as a 4-centre rearrangement or as a 1,3-sigmatropic shift (XIV⟶ XV). Likewise, the thermally induced rearrangement of imino-ethers[56,57] (XVI⟶ XVII) may be thought of as a 4-centre rearrangement (or, again, as a 1,3-shift). The kinetics of this rearrangement have been shown to be of first order and "mixing experiments" have indicated, by the absence of crossed products, that it is intramolecular. A related rearrangement (1⟶ 3 migration from oxygen to nitrogen) is that of alkyl cyanurates to alkyl isocyanurates[58-60].

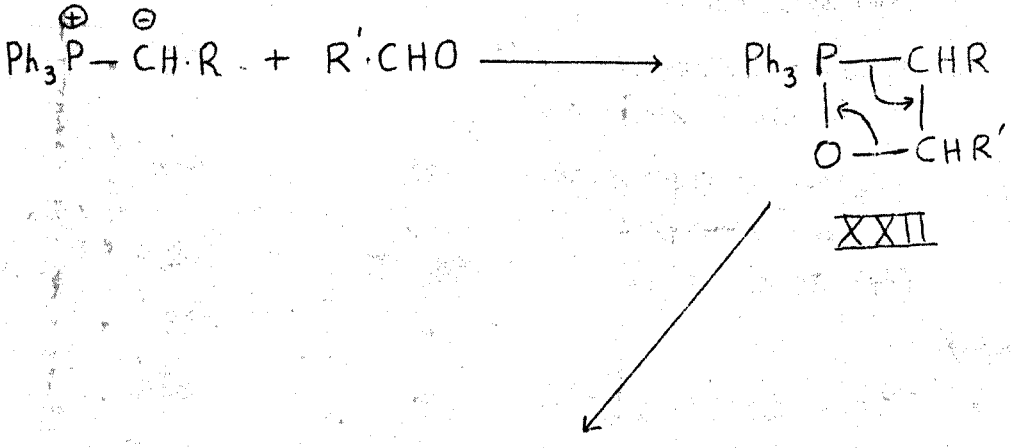
Clearly, depending on the atoms represented by X, Y and Z in the general rearrangement (XVIII⟷ XIX), a whole family of such migrations could well exist (see Table II).



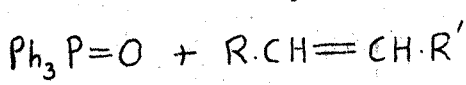
XVIII XIX



XX XXI



XXII



XXIII

TABLE II

R–X–Y–Z	REARRANGEMENTS	REFERENCES	ΔG^{c} (Kcal/mole^{-1})
R–C–N=O	R=H, isomerism of nitrosoalkanes to oximes	61	-5.9
R–O–C=C	(i) R=C, enol ethers to ketones; Fries rearrangement; Dihydrofuran to cyclopropyl aldehyde[a]	62, 63 64, 65	+27.4
	(ii) R=H, Enols to ketones	66	+11.3
R–O–C=N	Imino-ethers to amides	67, 68	+6.6
R–S–C=N	Thiocyanates to isothiocyanates	69	
R–N–N=O	N-nitroso-amides to diazonium carboxylates[b]	70	
P–N–N=O	N-nitrosophosphoramidates to diazonium phosphates[b]	38	+3.0
P–O–C=C	(i) Enol phosphates to ketophosphonates	71	+8.3
	(ii) Reverse of (i)	72, 73	-8.3
P–N–C=C	-	-	+23
P–C–N=O	Oxime phosphates[74]	-	+4.2
P–N–C=O	Imidoyl phosphates	-	+14.7

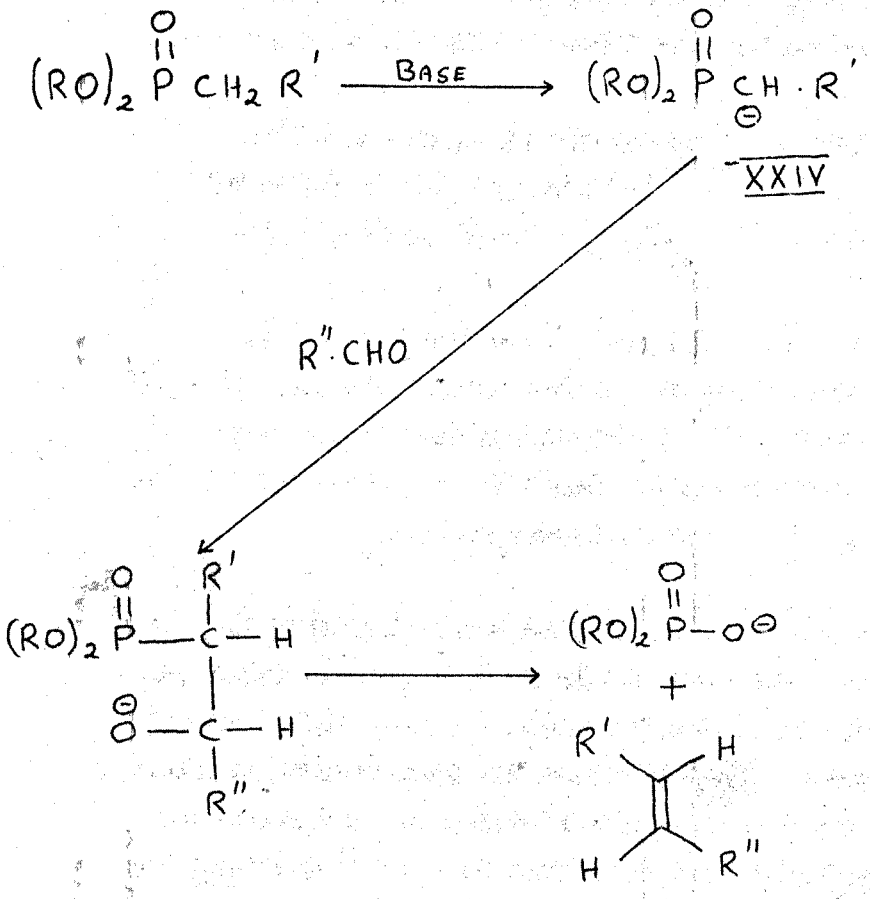


FIGURE VI

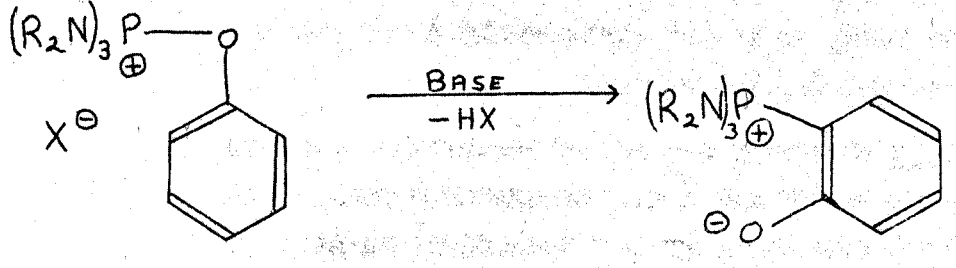
Notes: (a) This reversible rearrangement is probably facilitated in one direction by the relief of ring strain on expanding a three-membered to a five-membered ring (XX⟶ XXI)[154], and in the reverse direction by the bond-energy term.

(b) Further rearrangement of R.CO.O-N=N-R^1 to R.CO.O$^-$ $\overset{+}{N}_2$-R^1 is favoured, as is P-O-N=N-R^1 to P-O$^-$ $\overset{+}{N}_2$-R, by a large entropy term.

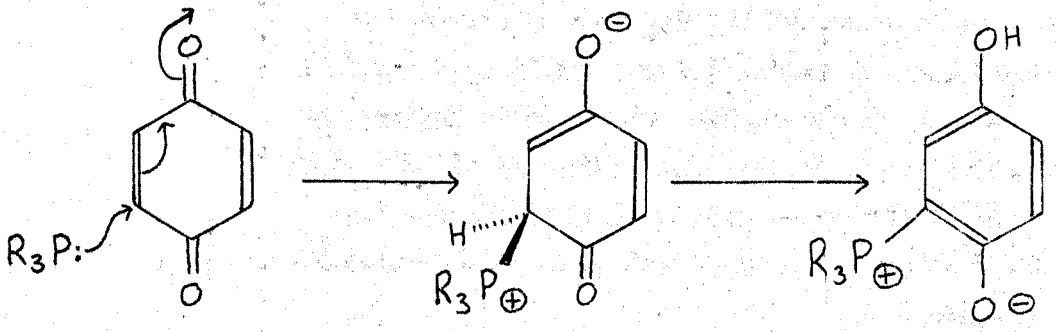
(c) The column headed ΔG refers to a simple calculation of the free energy changes involved based on the bonds broken and formed during rearrangement. This will be discussed in more detail in the following section.

4-centre rearrangements in phosphorus chemistry have been less well studied, the most widely studied example being the rearrangement of Wittig intermediates (XXII⟶ XXIII) as will be discussed later. This reaction can show stereospecificity; for example it has been found that whilst the intermediates derived from triphenyl phosphine lead to a mixture of cis and trans olefins, those derived from phosphonate anions (XXIV) lead almost entirely to trans olefins[75,76,220]. (Figure VI).

The observations of Machleidt and Strehlke[72] that β-keto-phosphonates can be isomerised to enol phosphates (see Table II) would seem to favour the reverse rearrangement, i.e. β-keto-phosphonate to enol phosphate. In view, however, of the



XXV XXVI



XXVII XXVIII

conversion (to a small extent) of enol phosphates to β-keto-phosphonates (see next section) under the catalytic influence of glacial acetic acid, it is not unreasonable to imagine an equilibrium between the two species.

The in vivo rearrangement of PEP requires no more than an equilibrium between PEP and 3-phosphonopyruvic acid, since removal of the latter (e.g. by transamination) would drive the reaction to completion. As 3-phosphonopyruvic acid is not known, in vitro tests of a possible reverse rearrangement are not possible.

The one reported case[71] (see Table II) of rearrangement of an enol phosphonium salt demonstrated its transformation, under the influence of strong base, to the enolate of the corresponding β-keto phosphonium salt (XXV $\longrightarrow$ XXVI).

Support for the frequent occurrence (though, perhaps, infrequent recognition) of 4-centre rearrangements in phosphorus chemistry, analogous to that undoubtedly occurring in the Wittig reaction, may be adduced from several lines of study. Ramirez[77] has shown that the interaction of trialkyl or triaryl phosphines with p-benzoquinone leads to the ylids (XXVIII). The favourable steric relationship between the carbonyl oxygen and the phosphonium centre in (XXVII) should assist P-O bond formation. Subsequent, or synchronous, prototopy would lead to one canonical form of the observed product. (Figure VII).

In contrast to this behaviour, interaction between trialkyl phosphites and p-benzoquinone led to a quinol phosphate (XXIX).[78-80] This reaction involves the "translocation" of an alkyl group. Small amounts ($\sim$10%) of the isomeric

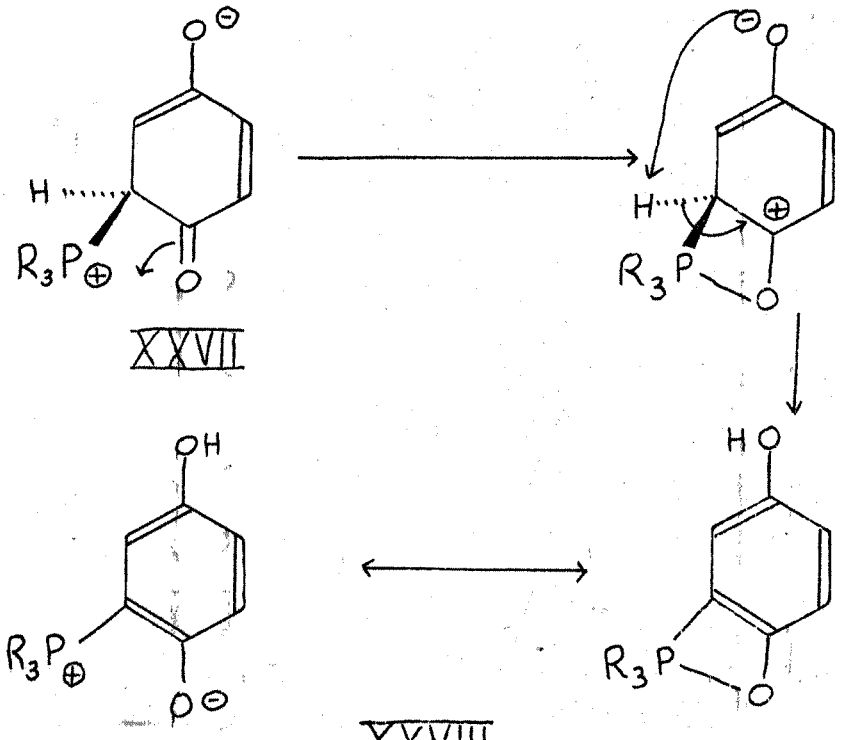
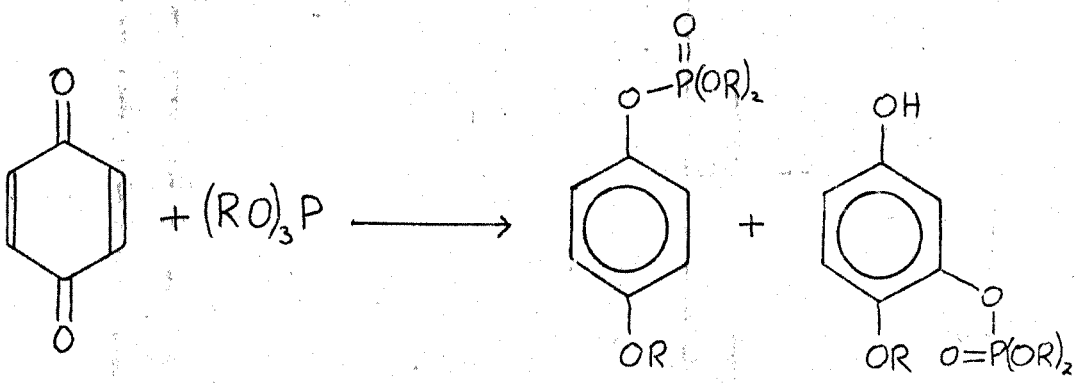

H
$R_3P\oplus$
XXVII
H
R_3P
OH
$R_3P\oplus$
H
R_3P
XXVIII

FIGURE VII


$+(RO)_3P$
$O-P(OR)_2$
OR
OH
OR
$O=P(OR)_2$
XXIX
XXX

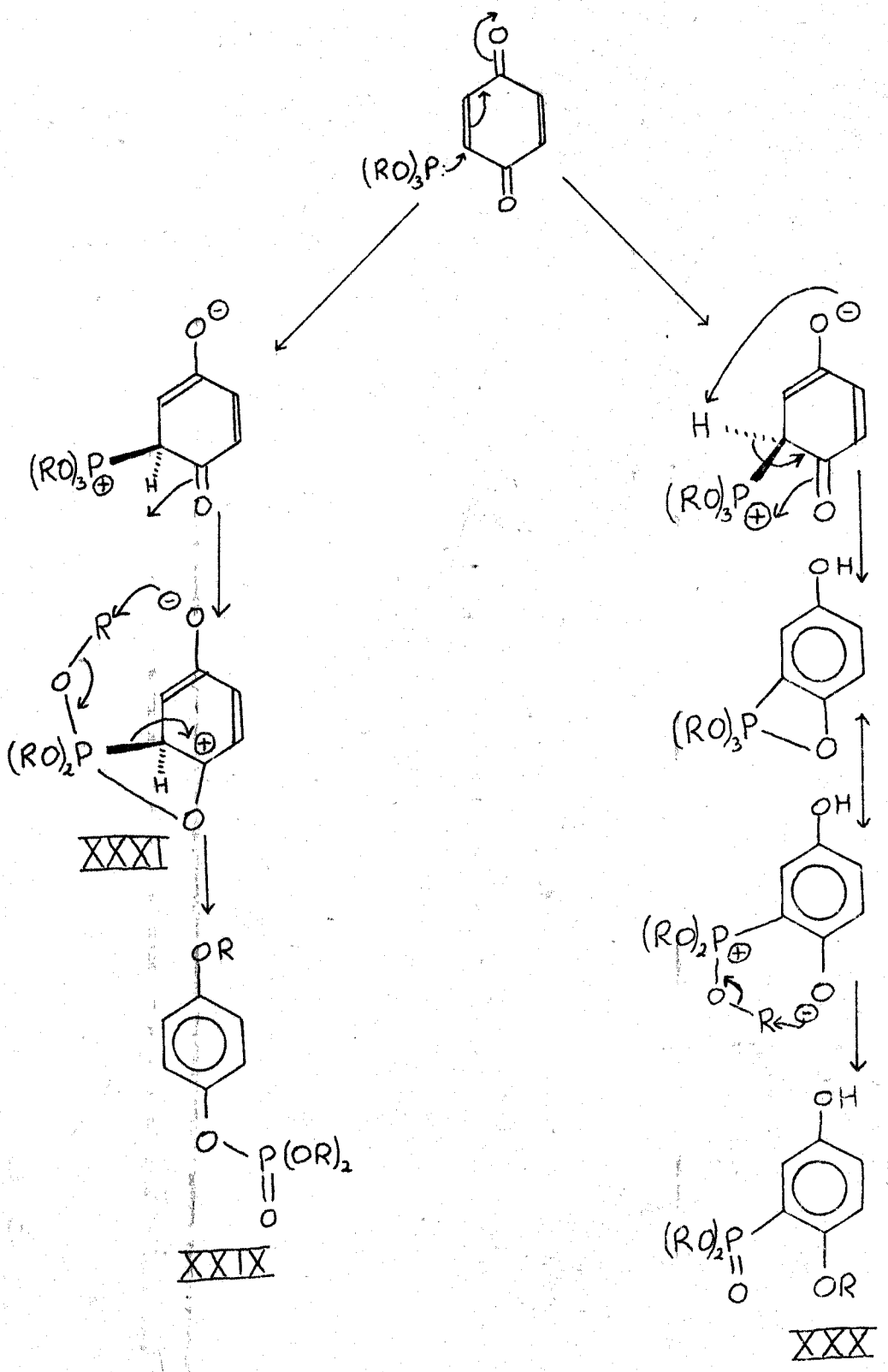
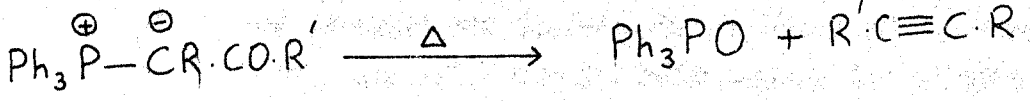

(RO)3P:
(RO)3P⊕
H
O
R
O
(RO)2P
H
XXXI
OR
O
P(OR)2
O
XXIX
H
(RO)3P⊕
O
H
(RO)3P
O
H
(RO)2P⊕
O
R
O
H
(RO)2P
O
OR
XXX

FIGURE VIII

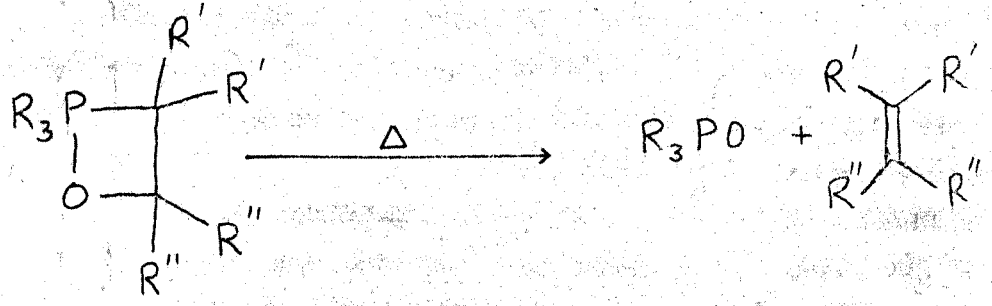


XXXII

R = -CO·R″, -C≡N, -Ar

R′ = -Ph

FIGURE IX



phosphonate (XXX) have been observed in this reaction[79]. Since both tertiary phosphines and trialkyl phosphites are nucleophilic reagents by virtue of the lone pair of electrons on phosphorus, the postulate of parallel behaviour in the initial step is not unreasonable (Figure VIII) (cf. The behaviour of trivalent phosphorus compounds with α-diketones, o-quinones, "activated" ketones and aldehydes [81]).

If, as indicated in Figure VIII, trialkyl phosphites behave as other tertiary phospherus species, the formation of two types of product is not unreasonable. Indeed, the initial report, by Russian investigators[82], cited (XXX; R=Et) as the chief product, quoting physical constants but advancing no spectroscopic evidence. Furthermore, an alternative synthesis of (XXIX; R=Et) showed it and (XXX; R=Et) to be dissimilar.

Evidence for 4-membered ring intermediates

4-membered ring structures like (XXXI) would appear to be very reasonable intermediates in a number of unrelated reactions in phosphorus chemistry.

Triphenyl phosphine acyl methylenes[83] (XXXII) on pyrolysis[84,85], yield acetylenes (Figure IX). By analogy with the thermal decomposition behaviour of 1,2-oxaphosphetanes[87], the intermediacy of a four-membered ring (XXXIII) would appear to be a reasonable route to the observed products (Figure X).

Structure (XXXIII), as indicated, represents one canonical form of the ylid. X-ray evidence[88] supports the dipolar structure (XXXIV; R=Cl or I), a conclusion with which NMR studies[212] of the compound (XXXIII $\longleftrightarrow$ XXXIV; R=H) are in reasonable agreement (see Appendix I). Decomposition of (XXXIII) would resemble decomposition of Wittig intermediates, an alkyne instead of an alkene being the product. Related

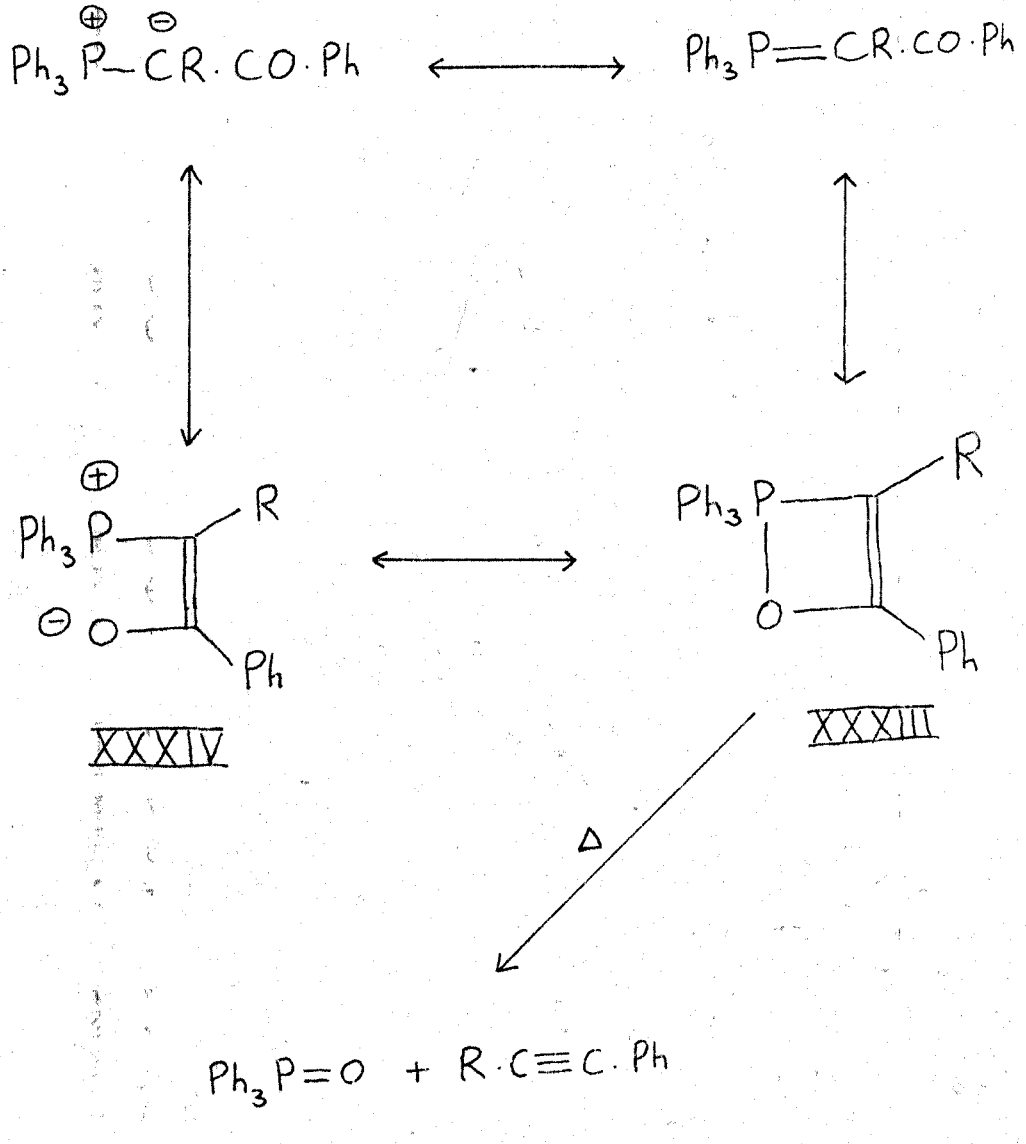
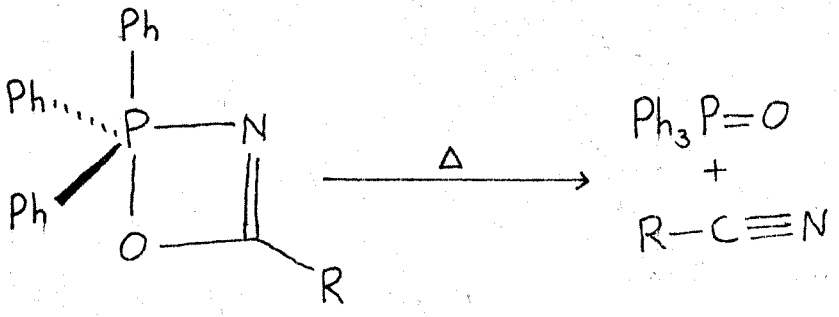
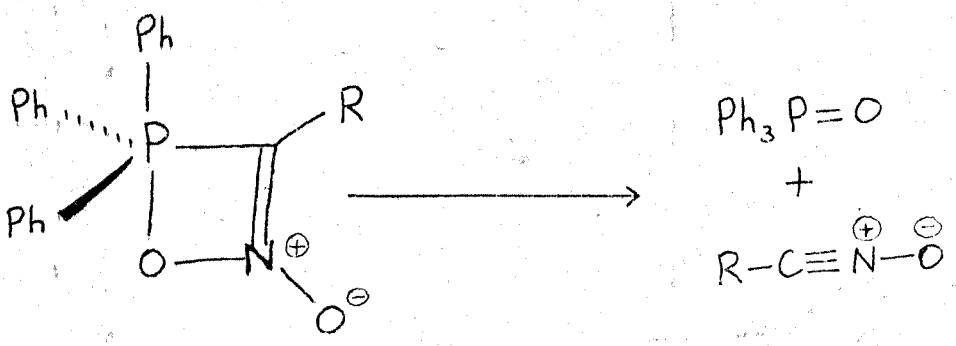

Ph3P⊕—⊖CR·CO·Ph
Ph3P=CR·CO·Ph
Ph3P⊕
R
⊖O
Ph
XXXIV
Ph3P
R
O
Ph
XXXIII
Δ
Ph3P=O + R·C≡C·Ph

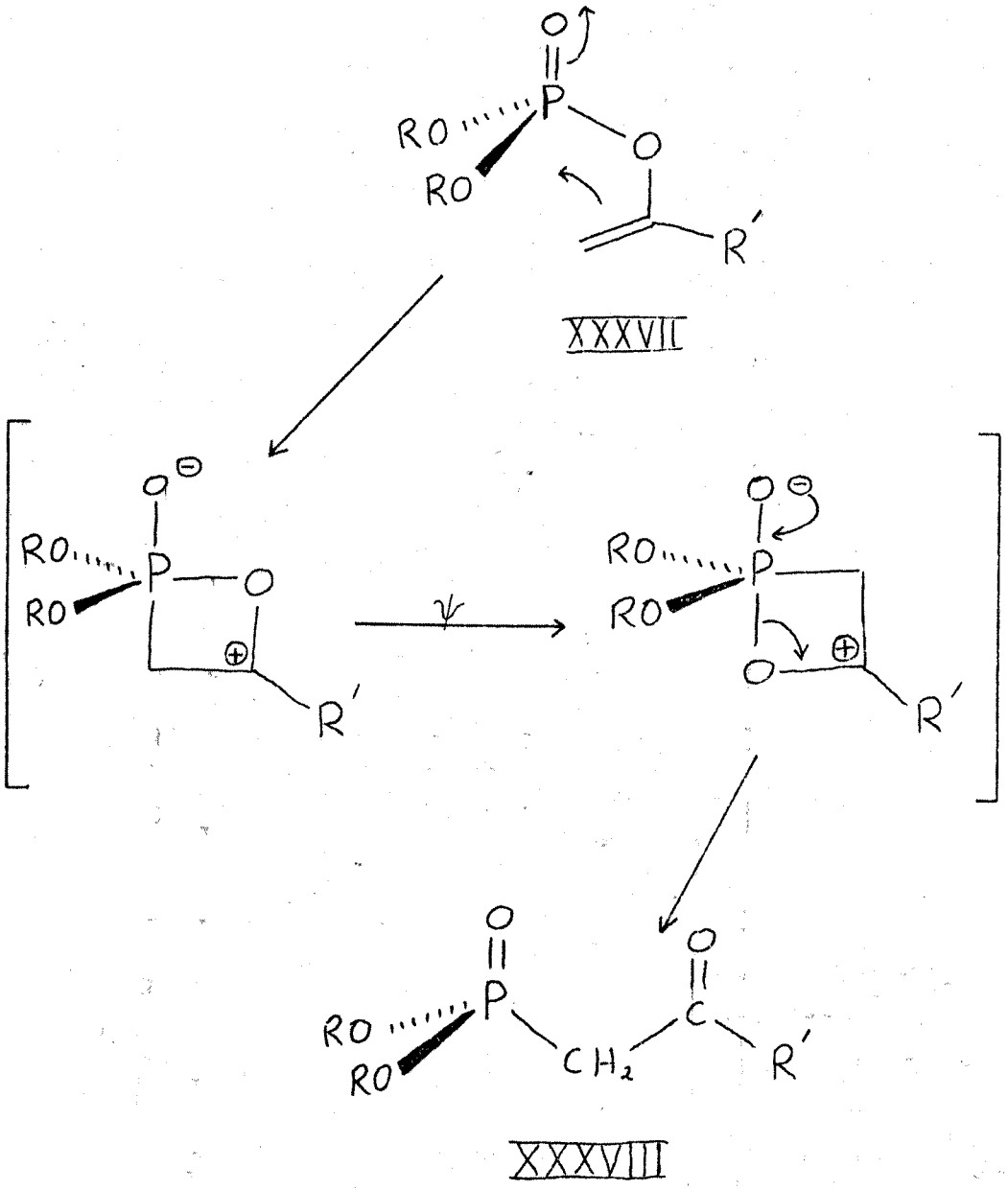
FIGURE X



XXXV

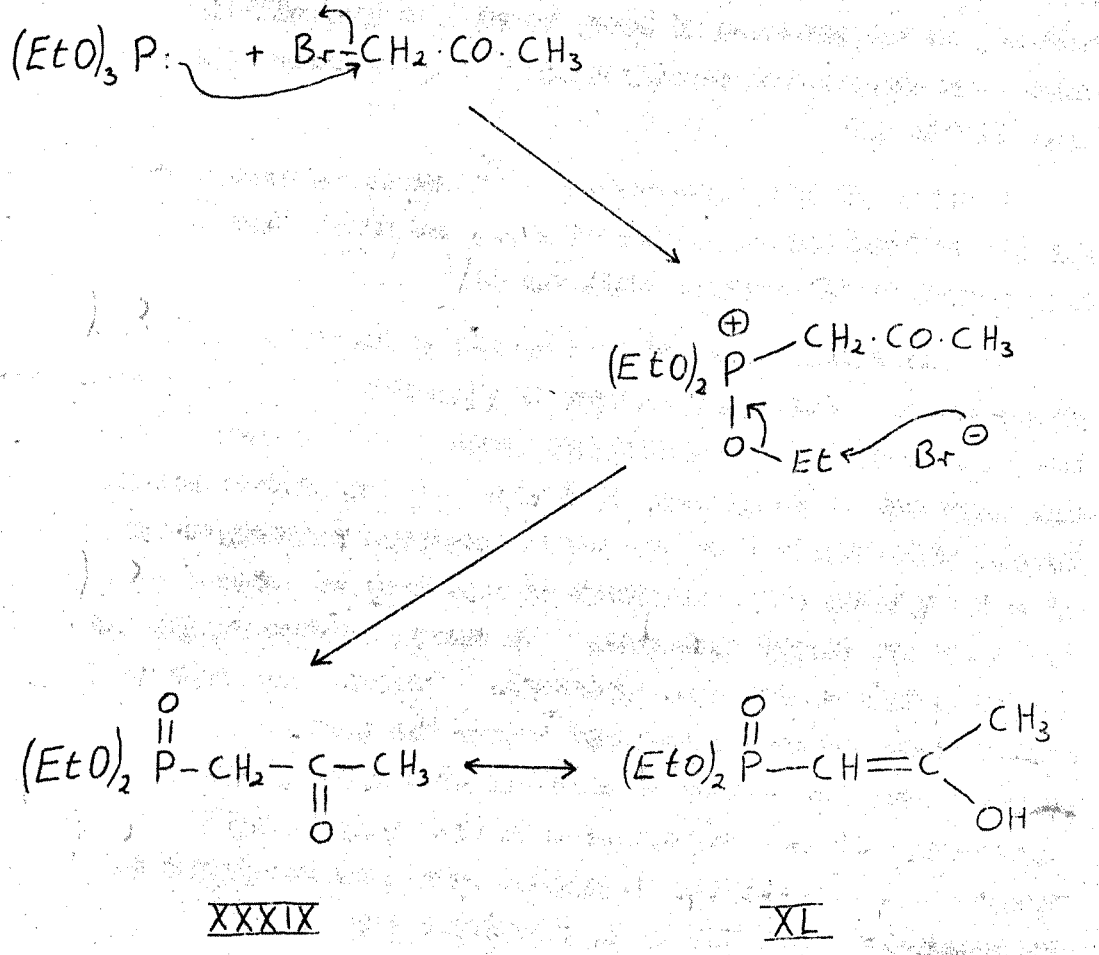


XXXVI



ψ = PSEUDOROTATION

FIGURE XI



XXXIX XL

decompositions have been reported by various workers. As long ago as 1921, Staudinger[89] discovered that the phosphine imine (XXXV; R=Ph), on pyrolysis, yielded triphenyl phosphine oxide and benzonitrile. Similarly, Horner et al.[90] have shown that dichlorotriphenyl phosphorane reacts with phenyl nitromethane, in the presence of base, to produce benzonitrile oxide - an observation readily explained by an intermediate like (XXXVI; R=Ph)[91].

A number of such observations[92,93] are of relevance here but a more detailed discussion of these and stereochemical considerations is deferred until the next section.

To summarise, the possible 4-centre rearrangement of enol phosphates to β-keto phosphonates (a plausible sequence is outlined in Figure XI) finds adequate analogy both in carbon chemistry and in phosphorus chemistry. In the carbon series, thermal, photochemical or Lewis-acid catalysed rearrangements of enol acylates (e.g. benzoates or acetates) to β-dicarbonyl compounds are direct analogies. In the phosphorus series the situation is somewhat more equivocal. However, not only do simple "free energy predictions" favour the 4-centre rearrangement but so also do a number of related 4-centre reactions. Of some significance in this respect and a factor which would gravitate against such a rearrangement is the seemingly high affinity of phosphorus for oxygen[94]. Hence phosphorus-oxygen bonds, once formed, seem difficult to break.

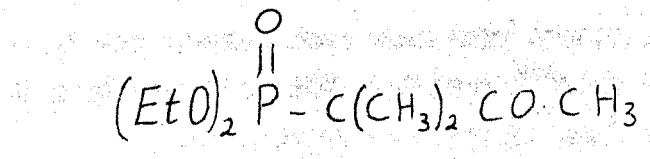
The relationship between (XXXVII) and (XXXVIII) is such that they are interconvertible by way of a 1,3-sigmatropic shift. Such a pericyclic reaction[95] may be the mechanistic description suitable for related rearrangements. 1,3-shifts over the O-C=C skeleton are well documented, particularly the rearrangements of enol ethers[64].

The phosphorus atom in phosphates is a "hard centre"[96]; likewise carbonyl oxygen is a "hard"nucleophile [97,98], whereas carbon acts as a "soft" nucleophile[97,98]. On this basis it would be predicted that the rearrangement of a β-keto-phosphonate to an enol phosphate ("hard" nucleophile attacking a "hard" centre) would be favoured over the reverse rearrangement ("soft"nucleophile attacking a "hard" centre). Such reasoning could account for the seeming reluctance of an "enol phosphate-β-ketophosphonate" rearrangement to occur. Hudson[99] has discussed these concepts in relation to the Perkow reaction.

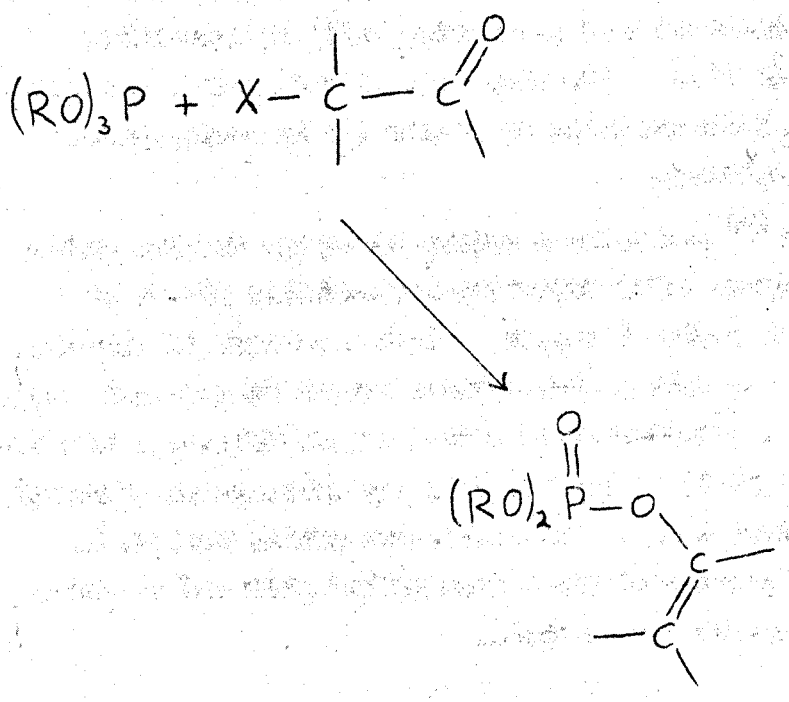
THE PERKOW REACTION

Historical background

In the years following the first reports of the Michaelis-Arbusov reaction[100,101], a very wide variety of organophosphorus compounds has been prepared in this manner. Several workers had attempted to use α-halo aldehydes, ketones and esters in this reaction and have assumed that the products were phosphonates[102]. However, in the reaction of certain α-haloketones, two products were reported[103]. From the reaction between triethyl phosphite and bromoacetone, Razumov and Petrov[104] obtained two isomeric products differing considerably in their physical properties. These workers assumed they had isolated the keto- and enol tautomers (XXXIX and XL) of the phosphonate. In attempts to study the assumed keto-enol tautomerism of such compounds, large numbers of products from the reaction of triethyl phosphite with α-bromo ketones were prepared[105]. The amount of "enol" was determined by titration with bromine. However, unusual results were obtained, e.g. 1,1-dimethyl-2-oxo propyl phosphonate (XLI) had an "enol" content of 23%.



XLI



XLII

In 1952, Perkow[106] was able to rationalise these observations by showing that the reaction of trialkyl phosphites with α-halo carbonyl compounds led to vinyl phosphates (enol phosphates, XLII).

It should be mentioned that some work carried out by the Shell Development Company[102] predated that of Perkow by a few years, though it remained unpublished until 1960.

Mechanistic studies

Various mechanisms have been proposed for the Perkow reaction since that advanced by Perkow, Krockow and Knoevenagel[107]. (Figure XII). The initial elimination of alkyl halide to give intermediates (XLIII, XLIV) which subsequently ionise (because of the inductive effect of the carbonyl group) to an ion-pair (XLV) and thence to enol phosphate (XLII) is improbable, especially in view of the mechanism of the Michaelis-Arbusov reaction (S_N2 displacement of halide ion by nucleophilic trialkyl phosphite).

Pudovik[108] suggested a cyclic mechanism for the Perkow reaction (Figure XIII) involving nucleophilic attack of phosphorus on carbonyl oxygen. Such a process is unlikely on two counts. Firstly, nucleophilic attack at carbonyl oxygen is improbable (the inductive effect of one halogen atom would not be expected to render the normally nucleophilic carbonyl oxygen electrophilic). Secondly, the cyclic process is depicted as proceeding via a sterically unfavourable seven-membered ring transition state.

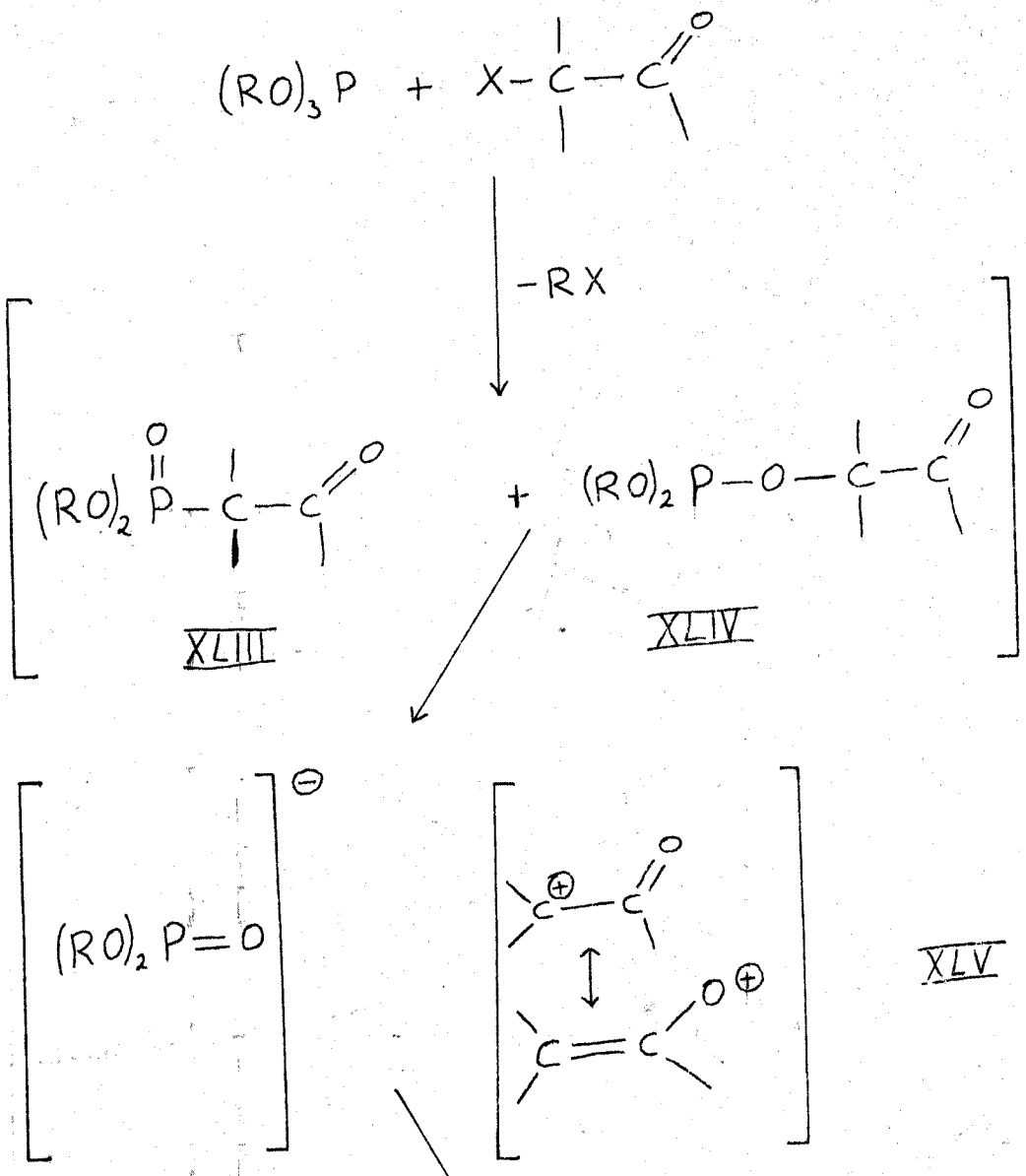
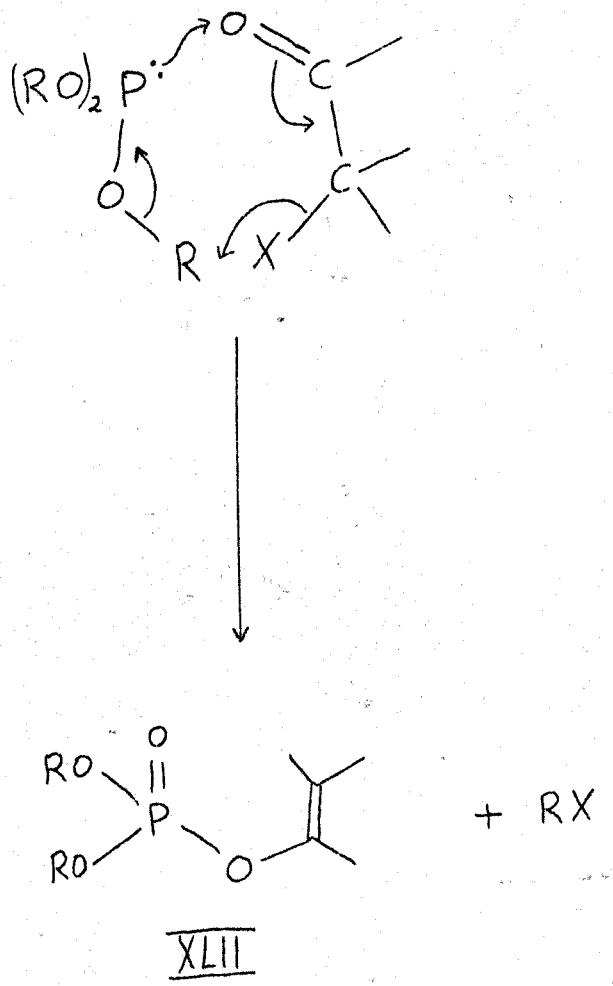

(RO)3P + X-C-C=O
-RX
(RO)2P-C-C=O
XLIII
+ (RO)2P-O-C-C=O
XLIV
(RO)2P=O
XLV
(RO)2P
XLII

FIGURE XII

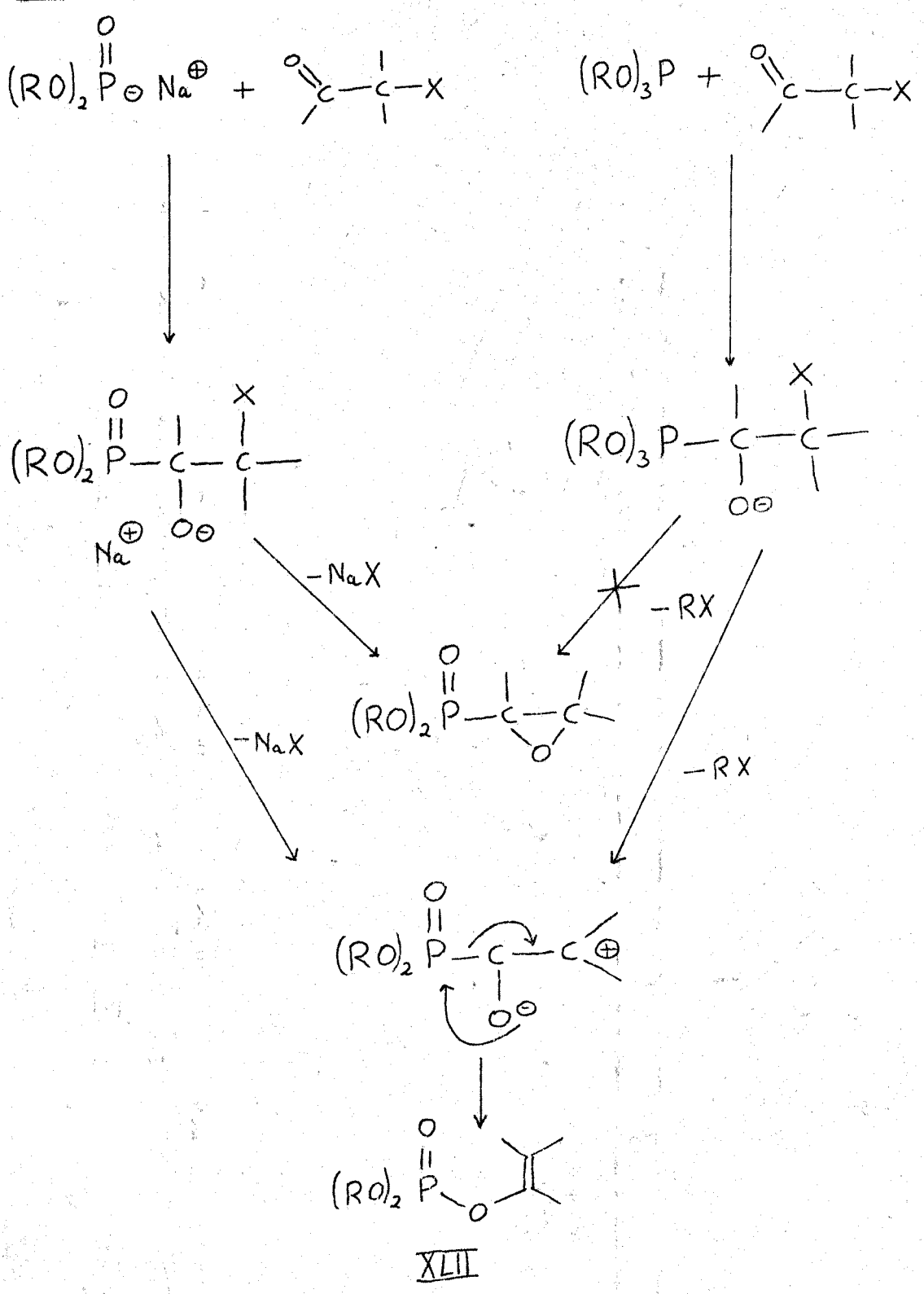


XLII

FIGURE XIII

MICHAELIS-BECKER REACTION

PERKOW REACTION



XLII

FIGURE XIV

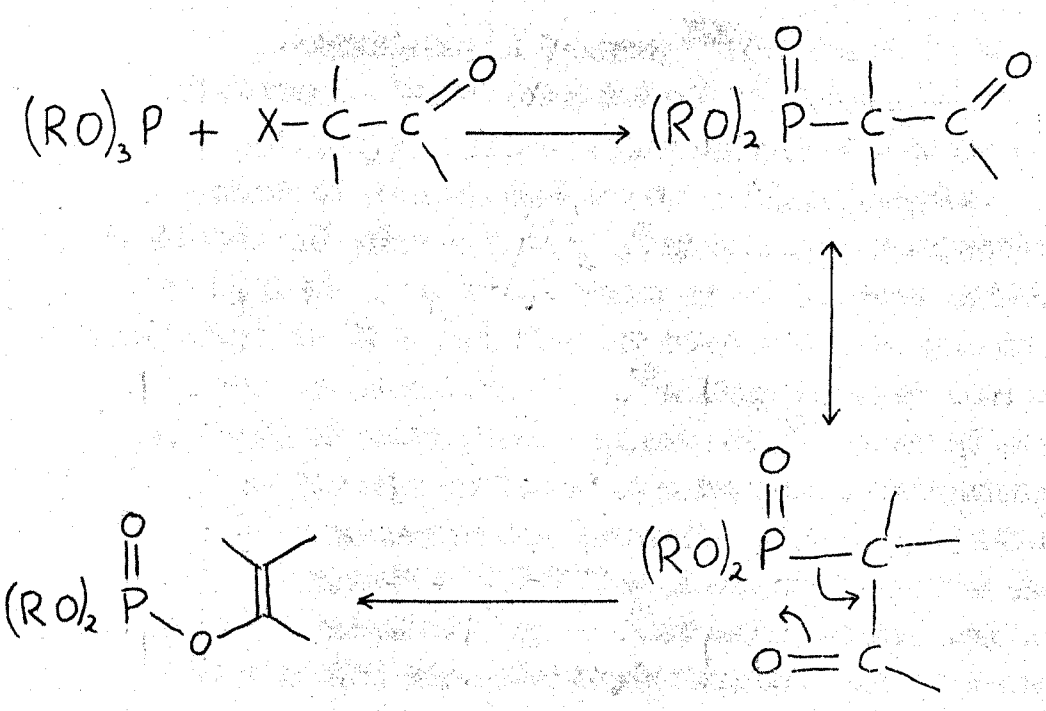


FIGURE XV

The initial step of the Kreutzkamp and Kayser mechanism[109] (Figure XIV), based on a common pathway for both the Perkow and the Michaelis-Becker[110] reactions, cannot be ruled out despite the fact that epoxides have never been observed as products in the Perkow reactions.

Spencer, Todd and Webb[111] proposed a "phosphonate-phosphate rearrangement" of the initially formed β-ketophosphonate, arising by a Michaelis-Arbusov reaction (Figure XV). However, β-ketophosphonates have not been observed to undergo this rearrangement very readily[73], if at all, under the conditions of the Perkow reaction, though rearrangement of a β-keto phosphonate to an enol phosphate under the influence of 2% orthophosphoric acid has been mentioned earlier[72]. A modification of this mechanism, by Cramer[112], is more attractive, since it postulates that rearrangement occurs prior to actual formation of the phosphonate (Figure XVI). Rearrangement is postulated as occurring in an intermediate like (XLVI). Dealkylation of (XLVI) without rearrangement leads to the phosphonate (XLVIII). Dealkylation of the rearranged phosphonium salt (XLVII) leads to the enol phosphate (XLII). The Cramer mechanism is particularly attractive in that it explains convincingly the increasing occurrence of the Michaelis-Arbusov reaction with the halogen atom in the order $Cl < Br < I$. It is suggested[112] that increased nucleophilicity of the halide ion leads to a greater proportion of dealkylation before rearrangement, resulting in a greater yield of phosphonate relative to phosphate.

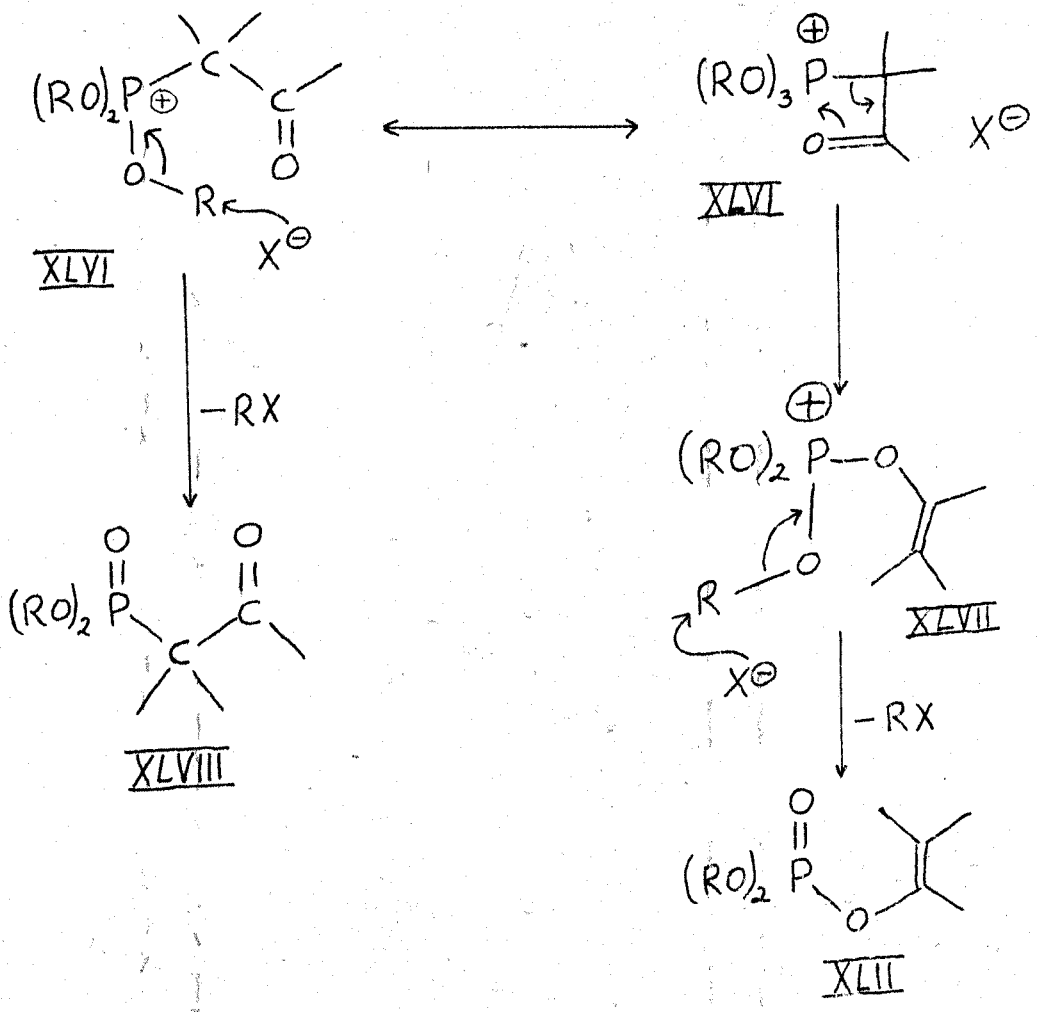


FIGURE XVI

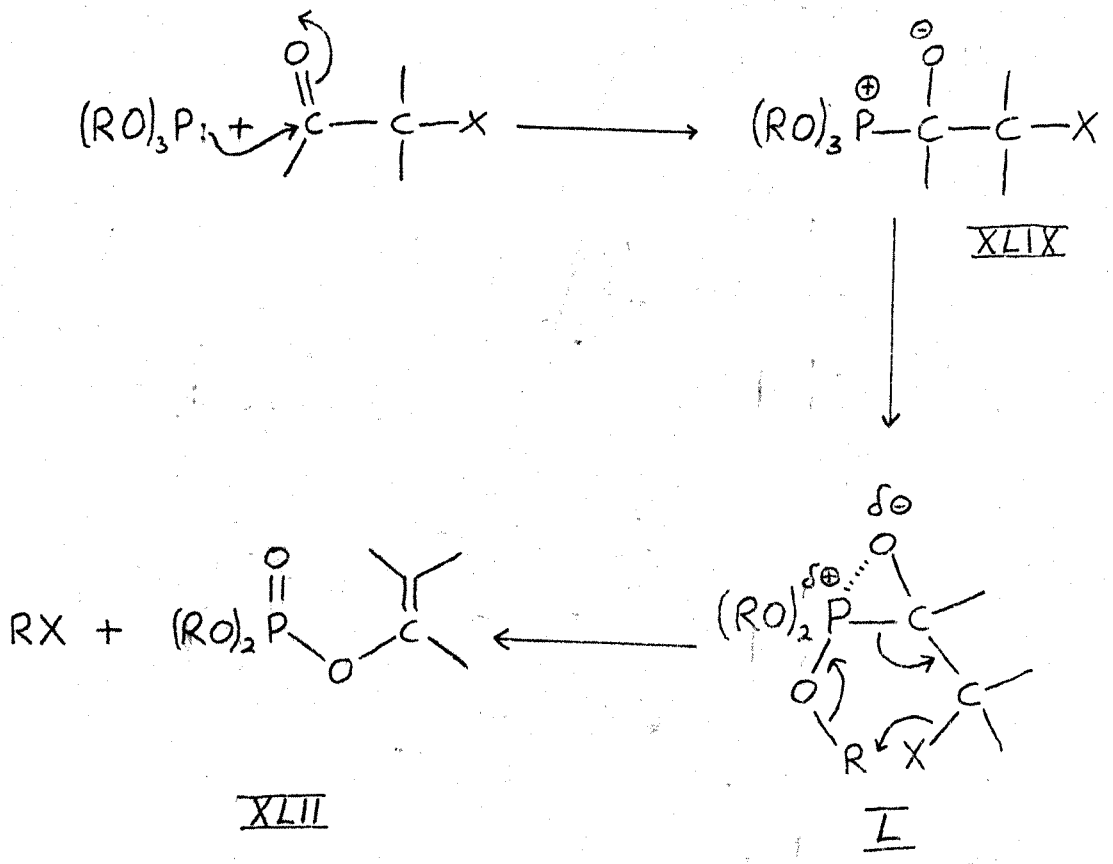


FIGURE XVII

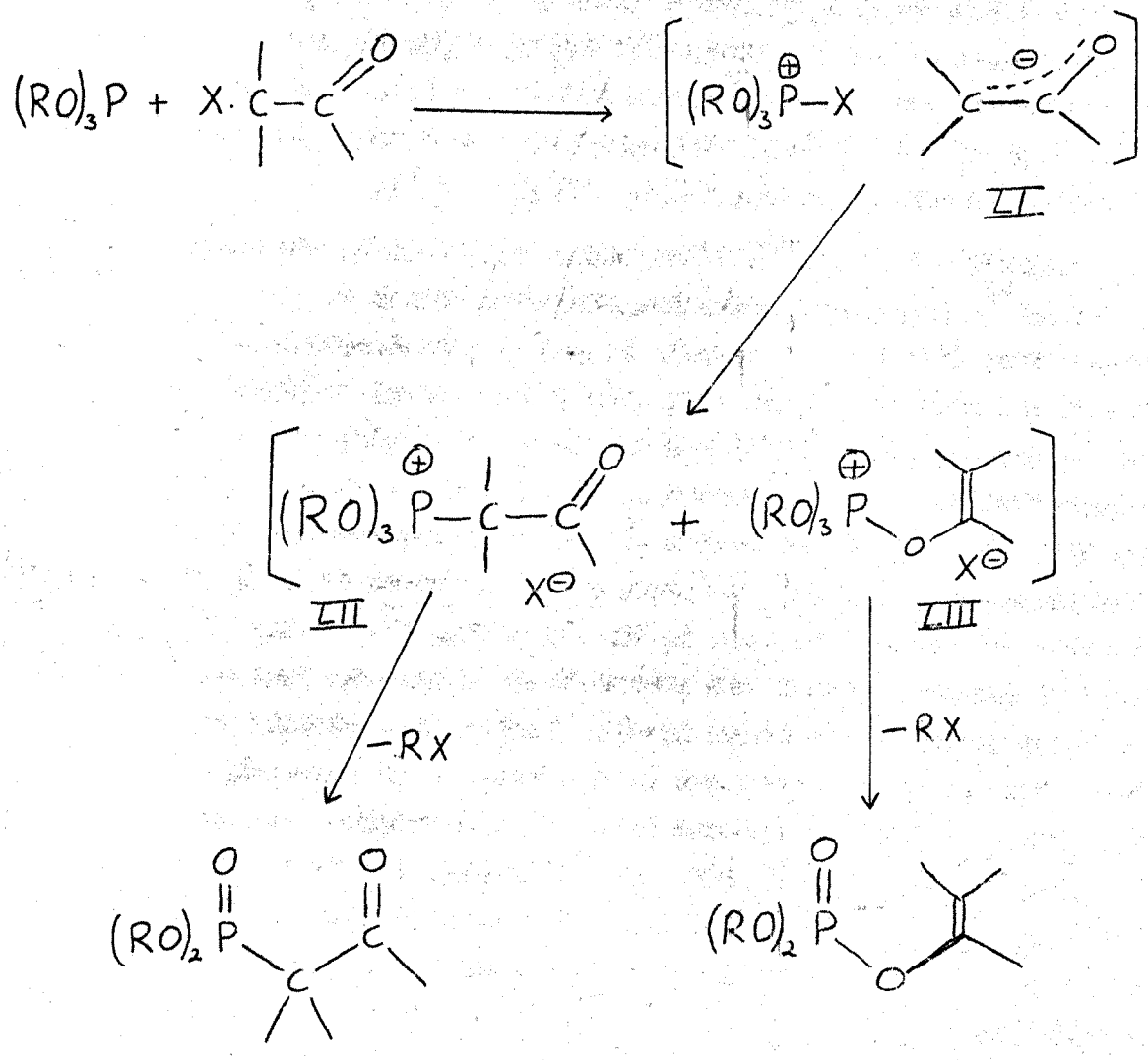
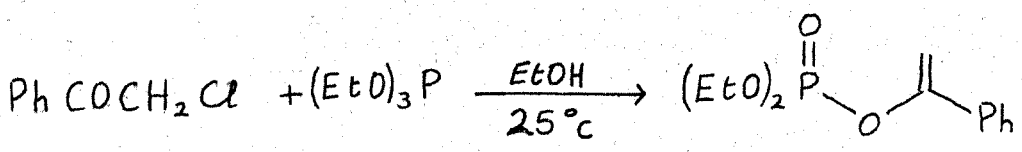


FIGURE XVIII

Another mechanism that has been proposed for the Perkow reaction was advanced independently by two groups, Allen and Johnson[113] and Kharasch and Bengelsdorf[114]. These authors envisaged nucleophilic attack of trivalent phosphorus on the carbonyl carbon to give an adduct (XLIX), the negatively charged oxygen of which subsequently attacked phosphonium phosphorus to form a quasi-three membered ring (L). Cyclic elimination of alkyl halide with synchronous P-C bond cleavage furnishes the enol phosphate XLII). (Figure XVII).

Speziale and Smith[115], subsequently supported by the work of Miller[116], proposed a mechanism involving attack at the halogen atom ("positive halogen") to give a halophosphonium-enolate ion pair (LI) which then undergoes internal displacement to the ions (LII, LIII) and subsequent dealkylation (Figure XVIII). This mechanism is unsatisfactory on two counts. Firstly, participation of the Michaelis-Arbusov reaction would be expected to increase in the order Cl>Br>I if attack at the halogen atom is the first step[117]. More powerful evidence against the intermediacy of enolate ions at any stage during the reaction is that derived from studies of the Perkow reaction carried out in the presence of hydroxylic solvents. Hudson[99,118] showed that reaction between triethyl phosphite and phenacyl chloride in the presence of ethyl alcohol at 25°C yielded 70% of the vinyl ester (LIV). Enolate anions would undergo a rapid solvolysis under these conditions to give dehalogenated ketone.

Very strong evidence for the initial attack of nucleophilic phosphorus at carbonyl carbon, leading to an intermediate (LV) was obtained by Clark and Kirby[119,120] who isolated fair yields



LIV 70%

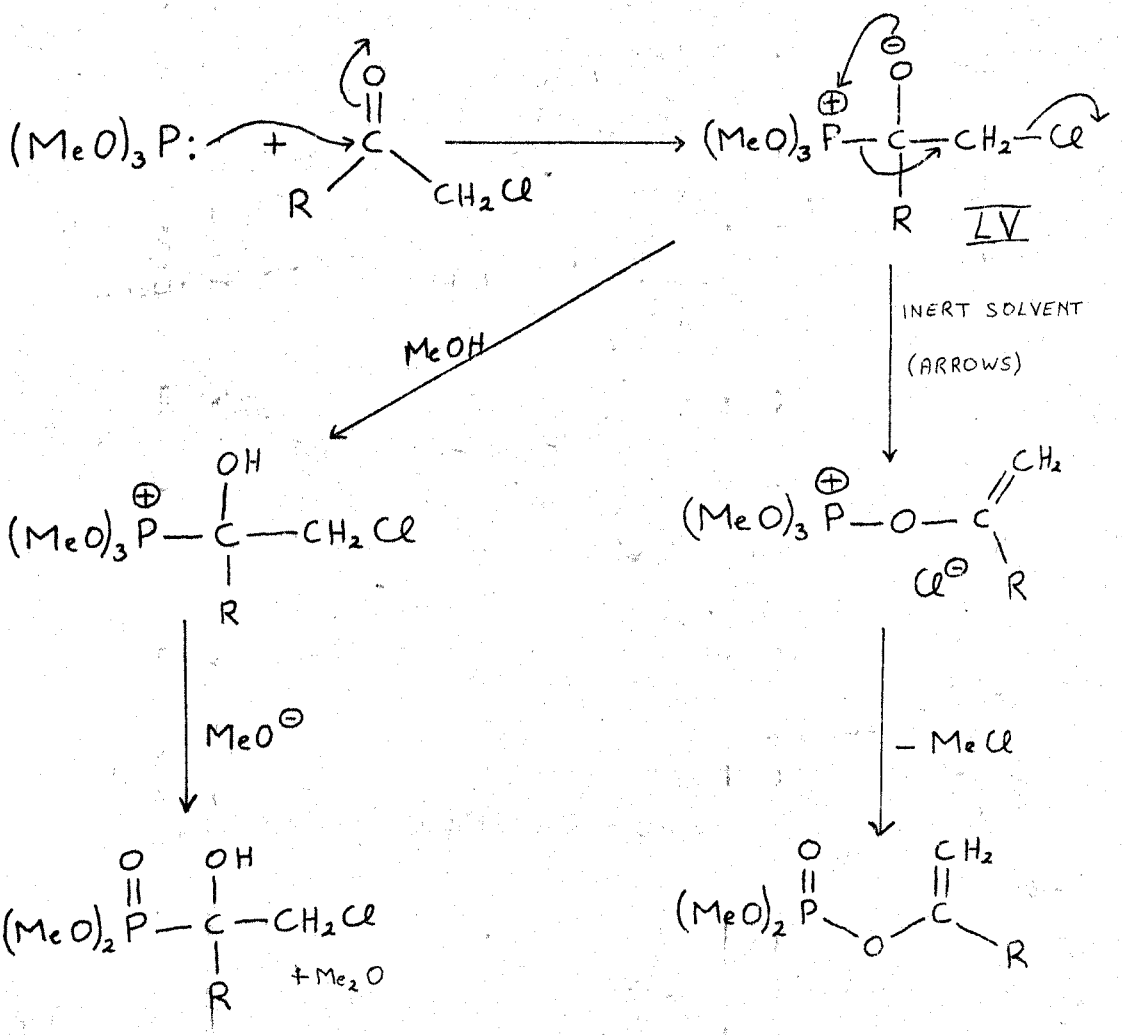


FIGURE XIX

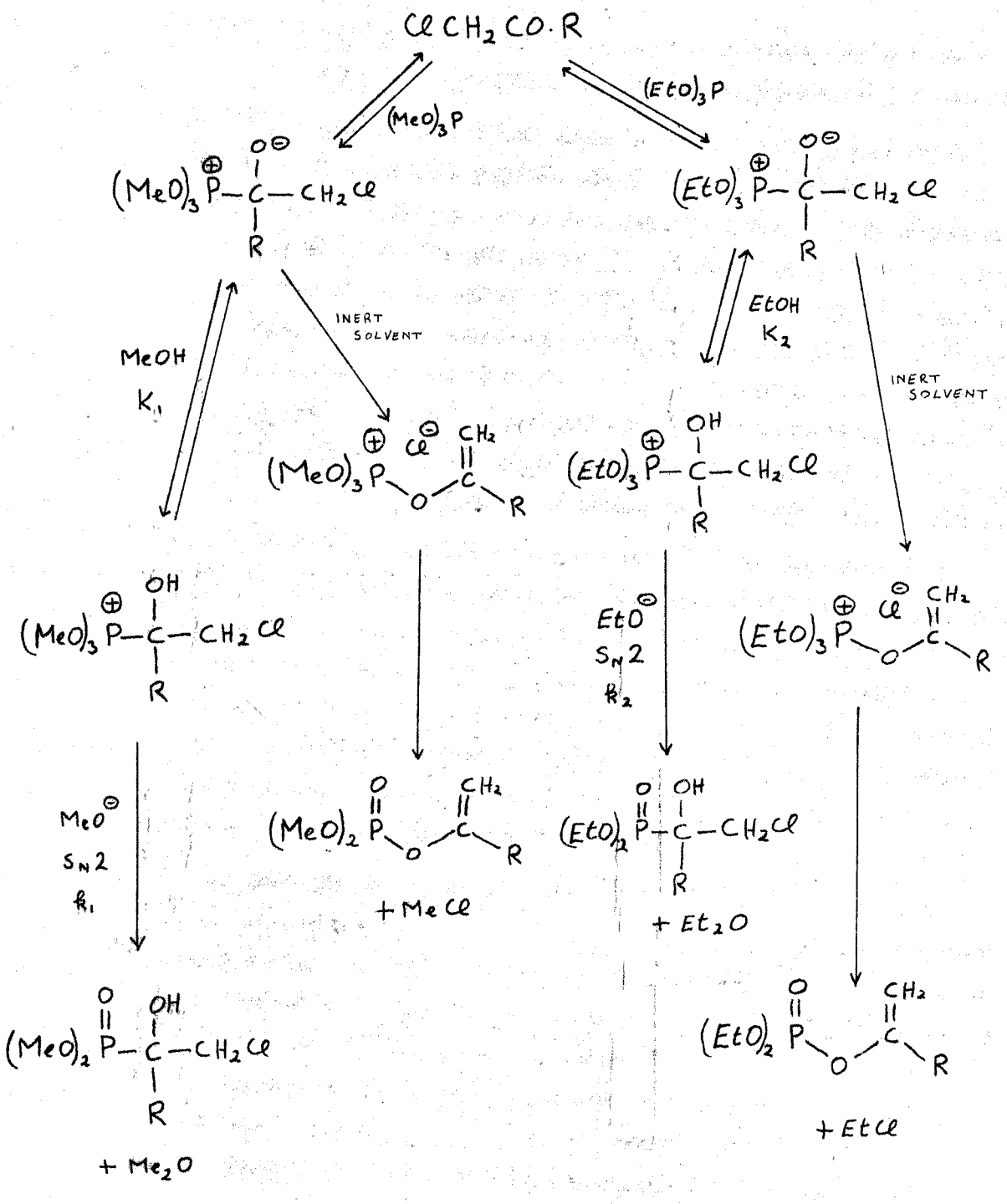

ClCH2CO·R
(MeO)3P
(EtO)3P
INERT SOLVENT
MeOH
K1
EtOH
K2
INERT SOLVENT
EtO⊖
SN2
k2
MeO⊖
SN2
k1
+ MeCl
+ Et2O
+ Me2O
+ EtCl

FIGURE XX

of α-hydroxy phosphonate esters from the reaction between chloroketones and trimethyl phosphite in methanol. (Figure XIX).

Conversely, reaction in ethanol was found to give high yields of enol phosphates[121]. The large changes in reaction path with relatively small changes in solvent were explained[120] by Figure (XX). It is argued that $K_1 > K_2$ since the pKa of methanol is 2.6 units lower than that of ethanol (methanol 16.7, ethanol 19.1[122]). Likewise, $k_1 > k_2$ since dealkylation of ethoxyphosphonium intermediates is known to be much slower than dealkylation of the corresponding methoxy intermediates. Hence $k_1K_1 \gg k_2K_2$ and in the case of the ethyl derivative, no appreciable amount of the α-hydroxy phosphonate is observed.

A recent report[123] of the reaction between trichloroacetyl thiourea and triethyl phosphite presents evidence for attack of the phosphite on positive chlorine as the initial step. This suggestion is not unreasonable in the case of trichloroacetyl thiourea, where not only is the carbonyl group hindered but the halogen atoms are also relatively positive. Furthermore, the carbanion (A) resulting from attack at chlorine would be capable of being stabilised by resonance as shown (Figure XXI, A $\longleftrightarrow$ E).

An interesting approach to the mechanism of the Perkow reaction has been discussed by Hudson[99]. The basic concept is that of "soft and hard acids and bases" (SHAB) as elaborated by Pearson[98]. Essentially, it is argued that the phosphorus of trialkyl phosphites (a "soft" nucleophile) is more likely to attack sp^2 carbon (carbonyl carbon, a "soft" electrophilic centre) than carbonyl oxygen ("hard") or sp^3 carbon ("harder" than sp^2 carbon). Rearrangement of the initially formed adduct

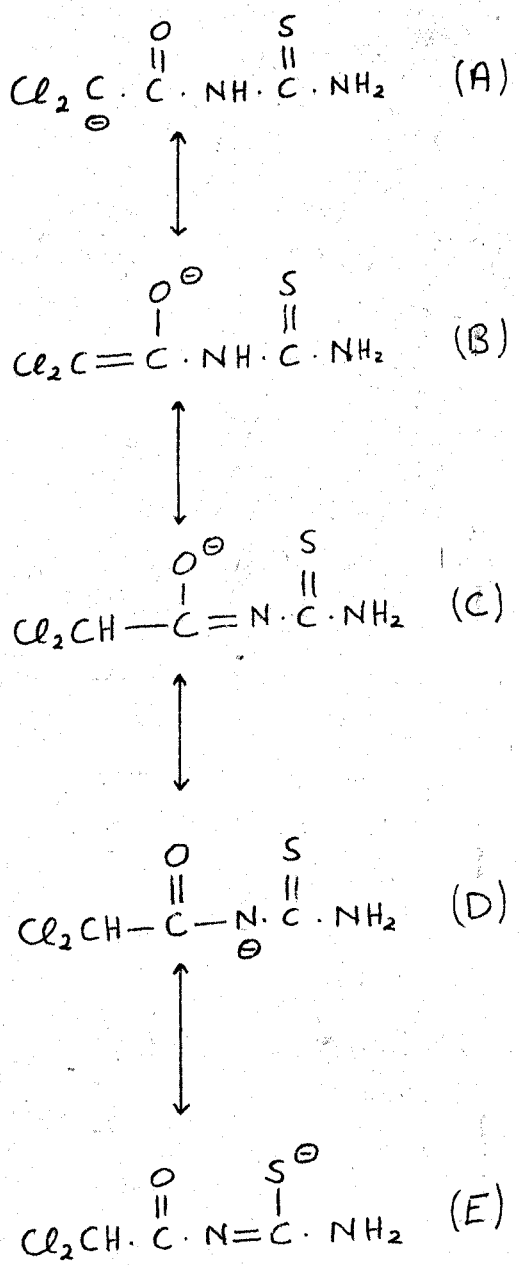


FIGURE XXI

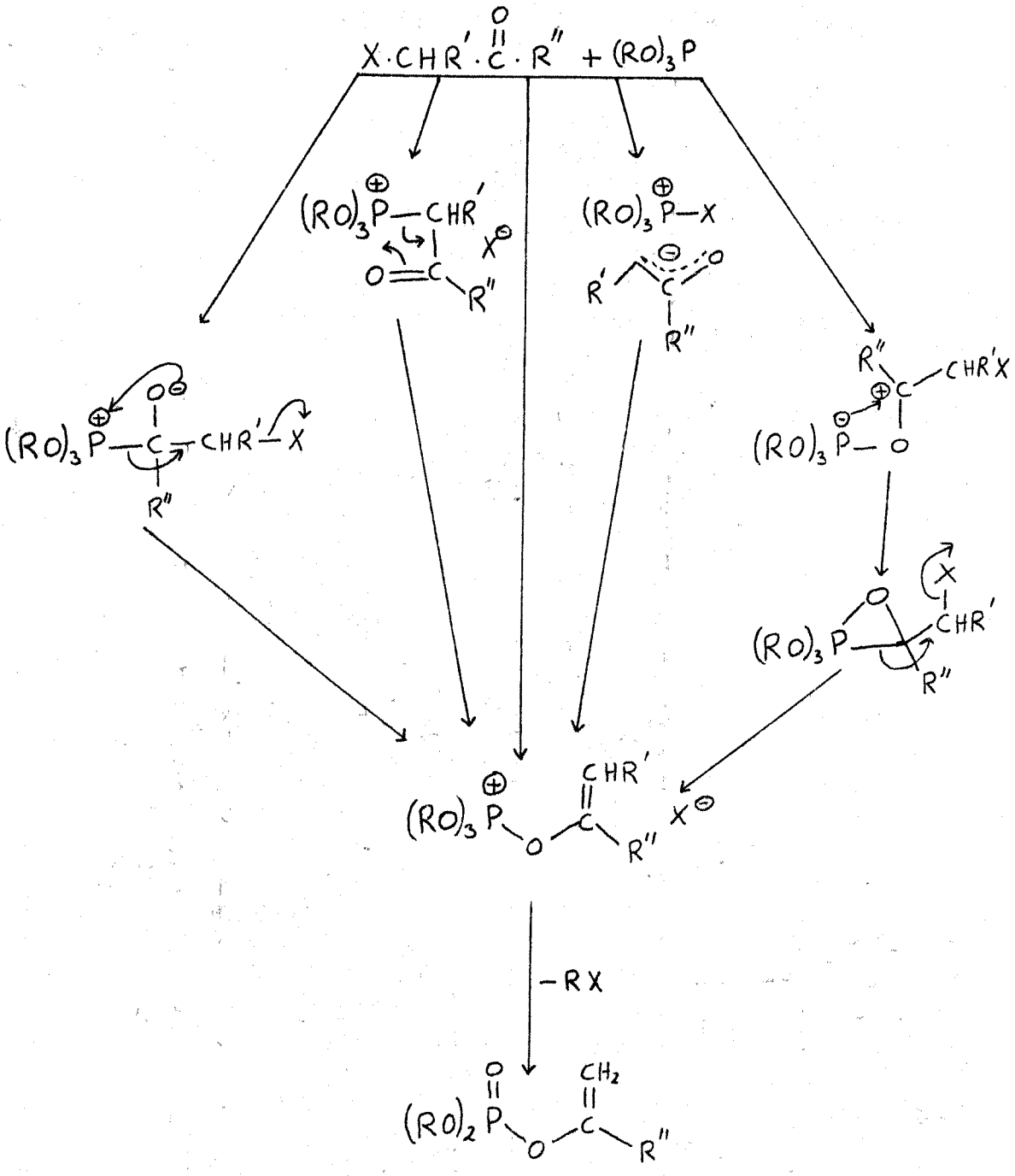
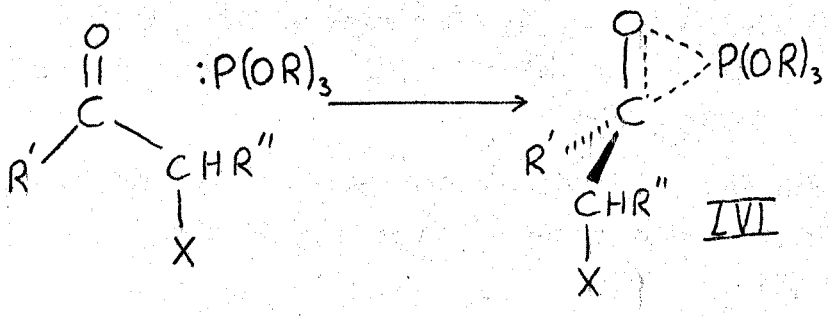
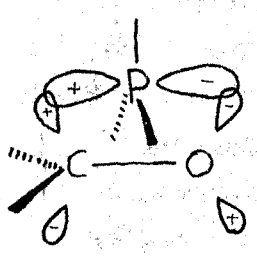

X·CHR′·C(=O)·R″ + (RO)3P
(RO)3P—CHR′
X⊖
R″
(RO)3P—X
R′
R″
(RO)3P—C—CHR′—X
R″
R″
CHR′X
(RO)3P—O
(RO)3P
X
CHR′
R″
(RO)3P
CHR′
X⊖
R″
−RX
(RO)2P
CH2
R″

FIGURE XXII

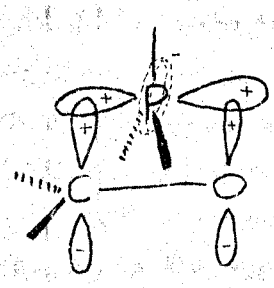


LVI



LVII

(P)$_{p_z}$ OVERLAP WITH (C=O)π^*



LVIII

(P)$_{d_{z^2}}$ OVERLAP WITH (C=O)π

FIGURE XXIII

(e.g. LV, Figure XIX) involves attack of a "hard" nucleophile ($\leftarrow O^-$) at a relatively hard electrophilic centre (R_4P^+), the product enol phosphonium salt and, subsequently, enol phosphate, being favoured by the "symbiotic" effect of several hard groups bonded to a hard central atom.

To summarise the mechanisms thus far proposed for the Perkow reaction, it is probably most useful to present them in schematic form (Figure XXII).

From the foregoing discussion it can be seen that all "merged mechanism" situations have been ignored. These are briefly outlined at this point for the sake of completeness.

1. "Three-centre" interaction with the carbonyl group (Figure XXIII) (LVI) represents a bonding situation between the carbonyl group and the phosphorus atom, the phosphorus being rehybridised to an sp^2 configuration. Overlap of the p_z orbital of phosphorus with the π^* lobes of the carbonyl group, with concomitant overlap of the lobes of the carbonyl group with the vacant d_z^2 orbital of phosphorus can be reasonably invoked as a $d_\pi - p_\pi$-bonding situation (LVII, LVIII).

2. Another hitherto unconsidered possible intermediate for the Perkow reaction is the "4-centre" transition state (LIX), representing an sp^3d-hybridised phosphorus atom interacting with both oxygen and carbon atoms in a 1,3 relationship. This intermediate, decomposition of which can occur in two ways as shown (Figure XXIV), can be considered as depicting a "frozen" phosphonate phosphate rearrangement.

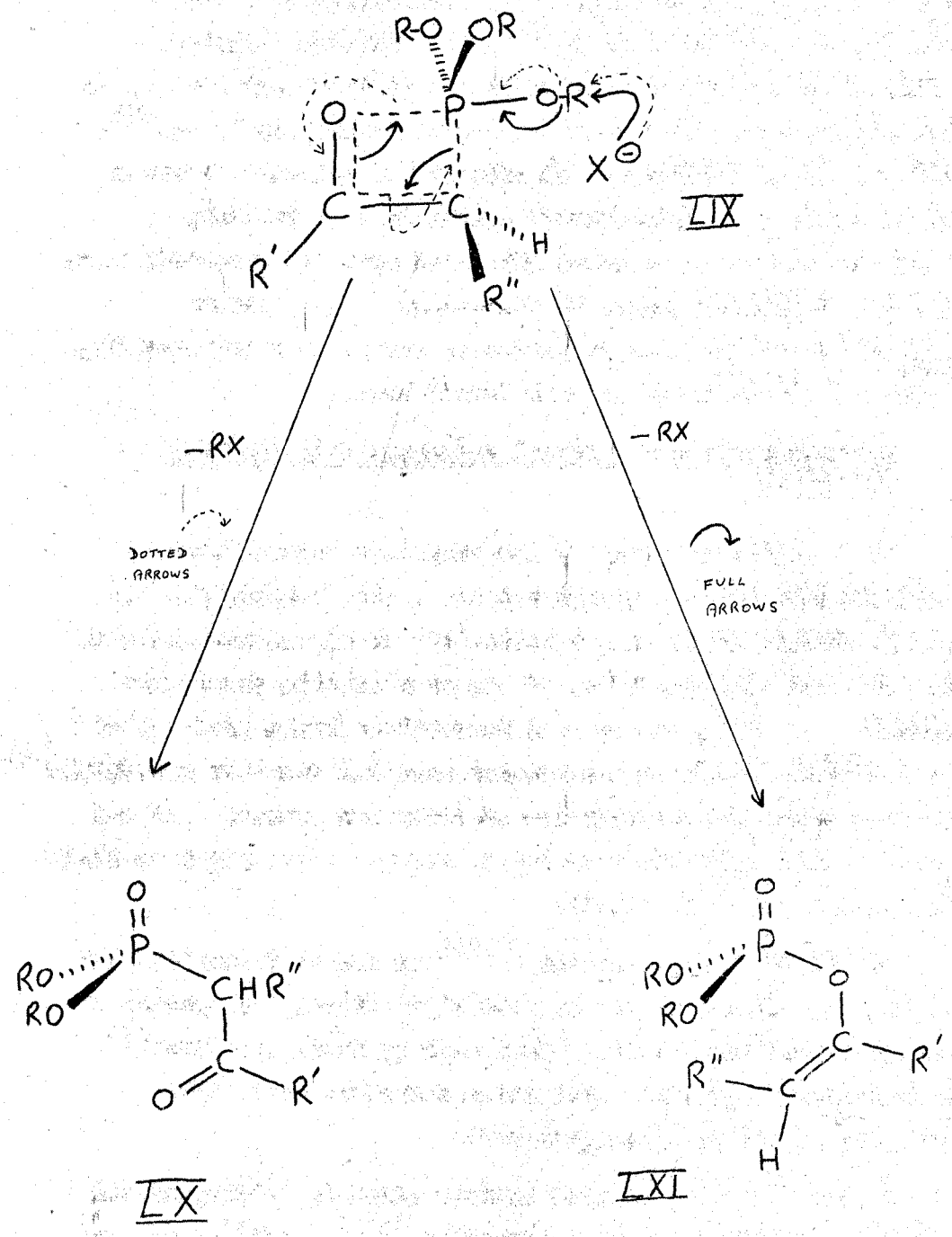

R-O
OR
O
P
O
R
X
C
C
H
R'
R''
LIX
-RX
DOTTED ARROWS
-RX
FULL ARROWS
O
P
RO
RO
CHR''
C
O
R'
LX
O
P
RO
RO
O
C
R''
C
R'
H
LXI

FIGURE XXIV

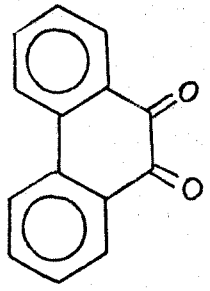
Mention should be made of the possibility that the Michaelis-Arbusov reaction leading to β-ketophosphonates occurs along a different mechanistic path from that leading to enol phosphates. This point has been stressed by Hudson[124]. Further, the possibility of an identity of behaviour between the reactions of α-halocarbonyl compounds with tertiary phosphites and those of other activated carbonyl compounds with tertiary phosphites cannot be dismissed. This latter possibility has provided the stimulus for some of our investigations and is discussed in some detail here.

Reactions of other carbonyl compounds with tertiary phosphites

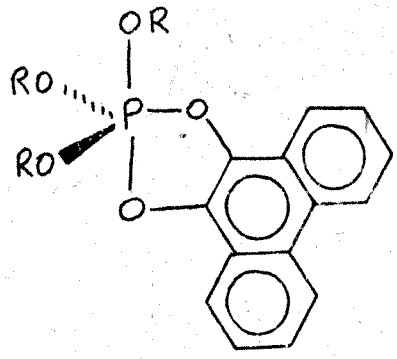
In an extensive study of the reactions between carbonyl compounds and tertiary phosphorus compounds, Ramirez and his co-workers have added very considerably to an understanding of the structure and properties of pentaco-ordinate phosphorus species. In 1960, the unusual properties of the products of the reaction between phenanthrenequinone and tertiary phosphites[125-8] led to a thorough investigation of their structures. It was shown[129] that these products had a trigonal bipyramidal pentaoxyphosphorane structure (LXII).

Subsequent investigations[127,128] showed that aromatic and aliphatic α-diketones also reacted with tertiary phosphites to form pentaoxyphosphoranes. Some work by Birum and Dever[130] is in complete agreement with these formulations of the structure of the products obtained.

A slow reaction occurred between aliphatic aldehydes and tertiary phosphites at room temperature[131] to yield compounds containing pentaco-ordinate phosphorus, in these cases as



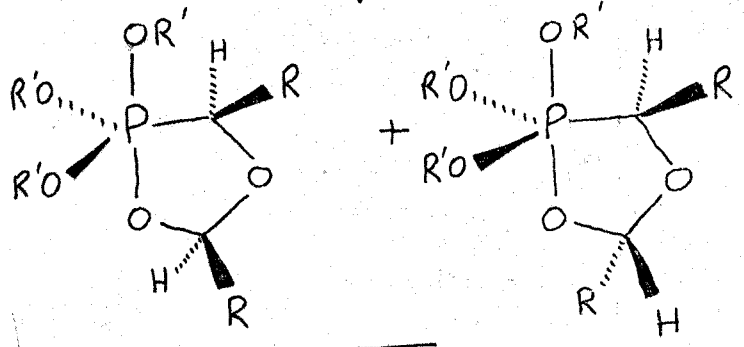
+ $P(OR)_3$



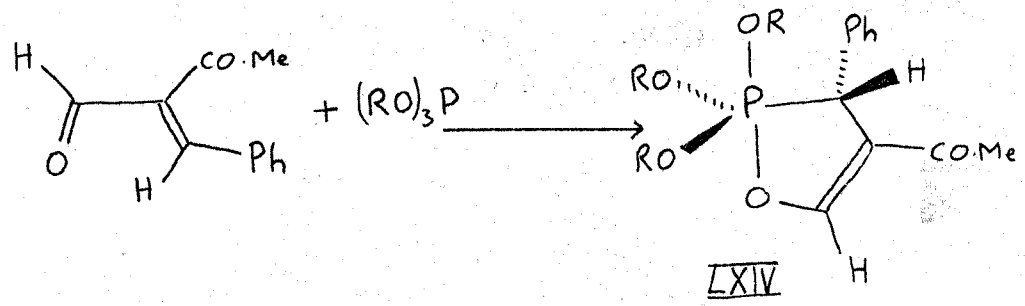
LXII

---

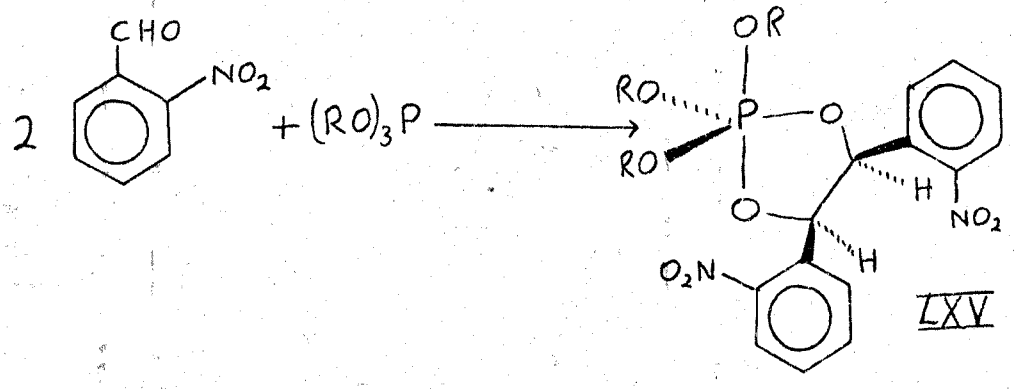
2. R.CHO + $(R'O)_3P$



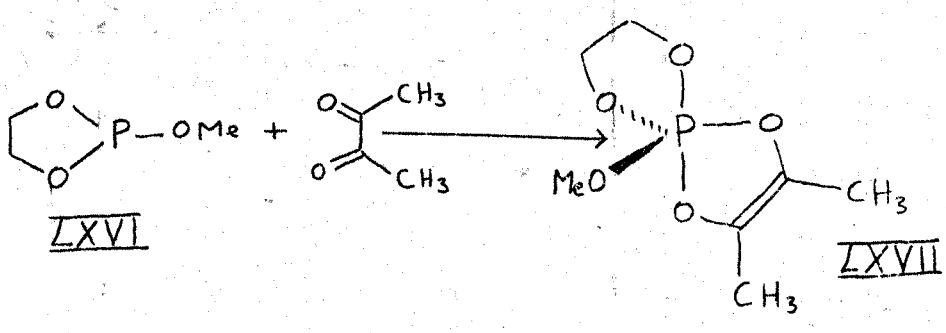
LXIII



LXIV

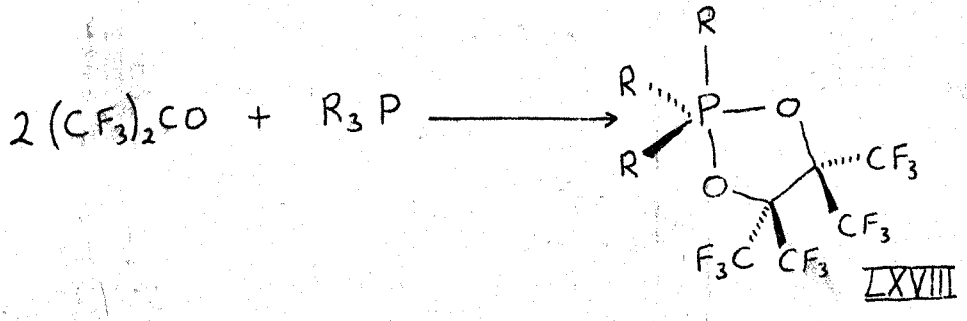


LXV

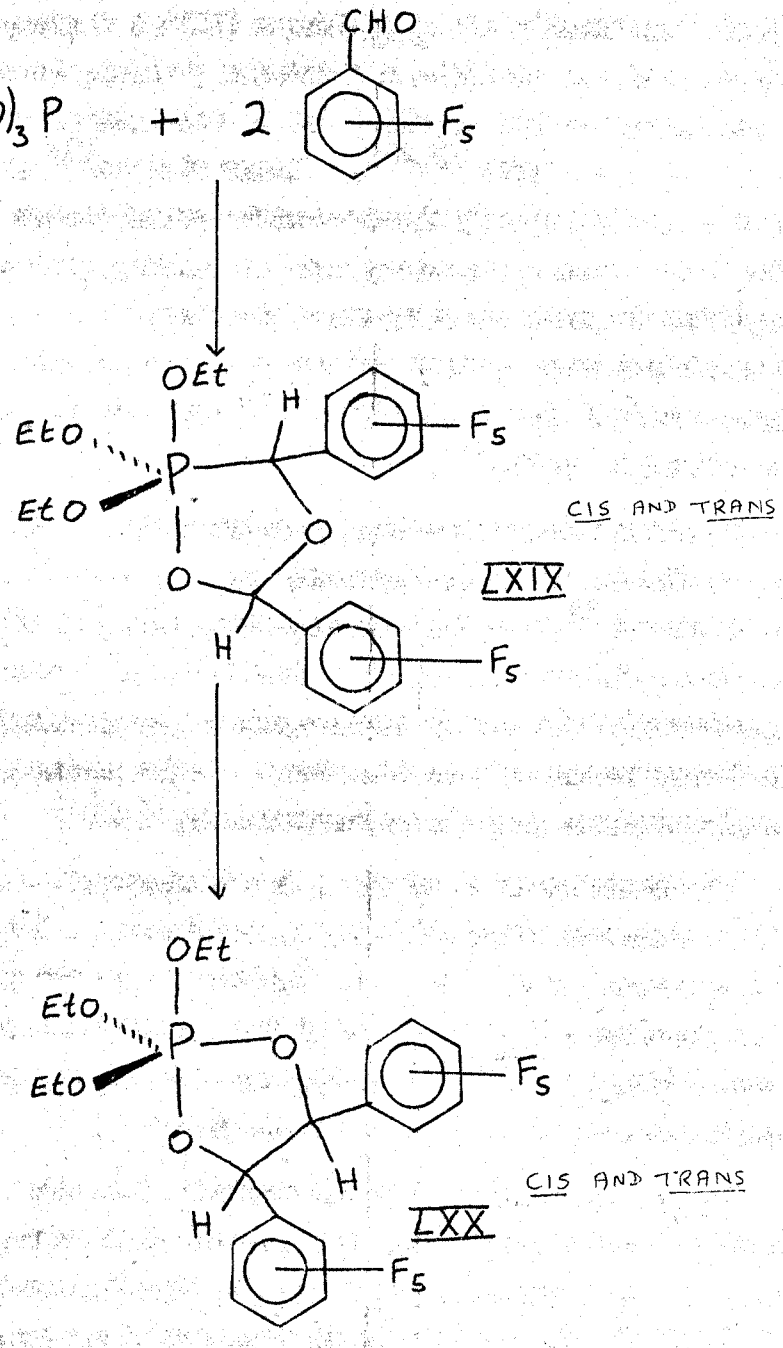


LXVI

LXVII



LXVIII

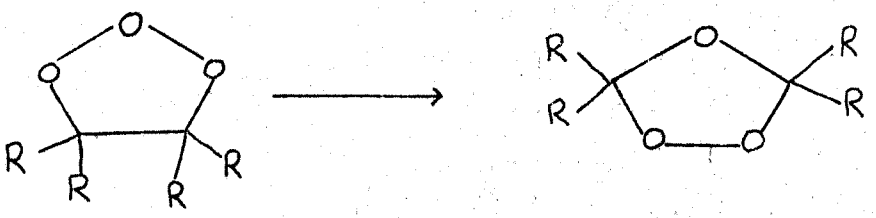

(EtO)3 P
+ 2
CHO
F5
OEt
EtO
EtO
P
H
O
O
H
F5
CIS AND TRANS
LXIX
OEt
EtO
EtO
P
O
O
H
H
F5
F5
CIS AND TRANS
LXX

tetraoxyalkyl phosphoranes (LXIII). The major isomer in these products was usually the meso-isomer (LXIII; R groups cis).[81] Reaction with α,β-unsaturated ketones (bearing an electron-withdrawing group on the α-carbon) led to unsaturated tetraoxyalkylphosphoranes (e.g. LXIV)[131,132]. Later studies[133] showed that aromatic aldehydes with electron-withdrawing groups in the ortho - or para - positions reacted readily with tertiary phosphites to yield pentaoxyalkyl phosphoranes (LXV). When the reactions were carried out using cyclic phosphites, e.g. ethylene methyl phosphite (LXVI)[134], spiro-oxyphosphoranes were obtained (LXVII)[134].

Reaction between tertiary phosphines and hexafluoroacetone led, similarly, to pentaoxyphosphoranes (LXVIII)[155]. It has been observed[136] that the corresponding reaction between pentafluorobenzaldehyde and triethyl phosphite led initially to a 1,4,2-dioxaphospholane (a tetraoxyalkyl phosphorane), (LXIX), this being converted into the final, stable product, a 1,3,2-dioxaphospholane (a pentaoxyphosphorane), (LXX).

The transformation of the 1,4,2-dioxaphospholane into the 1,3,2-dioxaphospholane skeleton is analogous to the transformation of a molozonide into the more stable "true ozonide" (LXXI ⟶ LXXII), as can be seen by a comparison of the skeletal arrangements involved (Figure XXV). Both systems effectively undergo a change of a -C-O- system to an -O-C- system.

The 1,3,2-dioxaphospholanes derived from alkyl phosphines and hexafluoroacetone were found to undergo a fundamental molecular rearrangement on heating, to give 1,2-oxaphosphetanes (LXXIII)[87]. Though these compounds were very sensitive to moisture they were shown to be very stable in dry atmospheres.

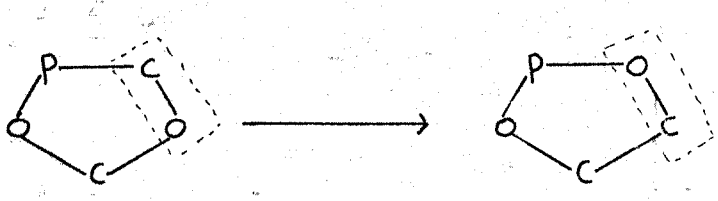


MOLOZONIDE

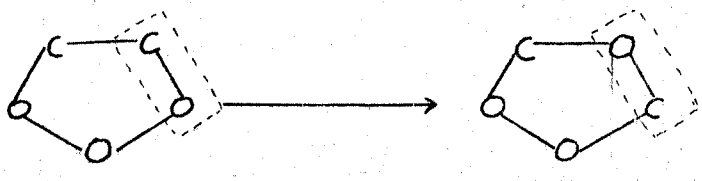
LXXI

TRUE OZONIDE

LXXII

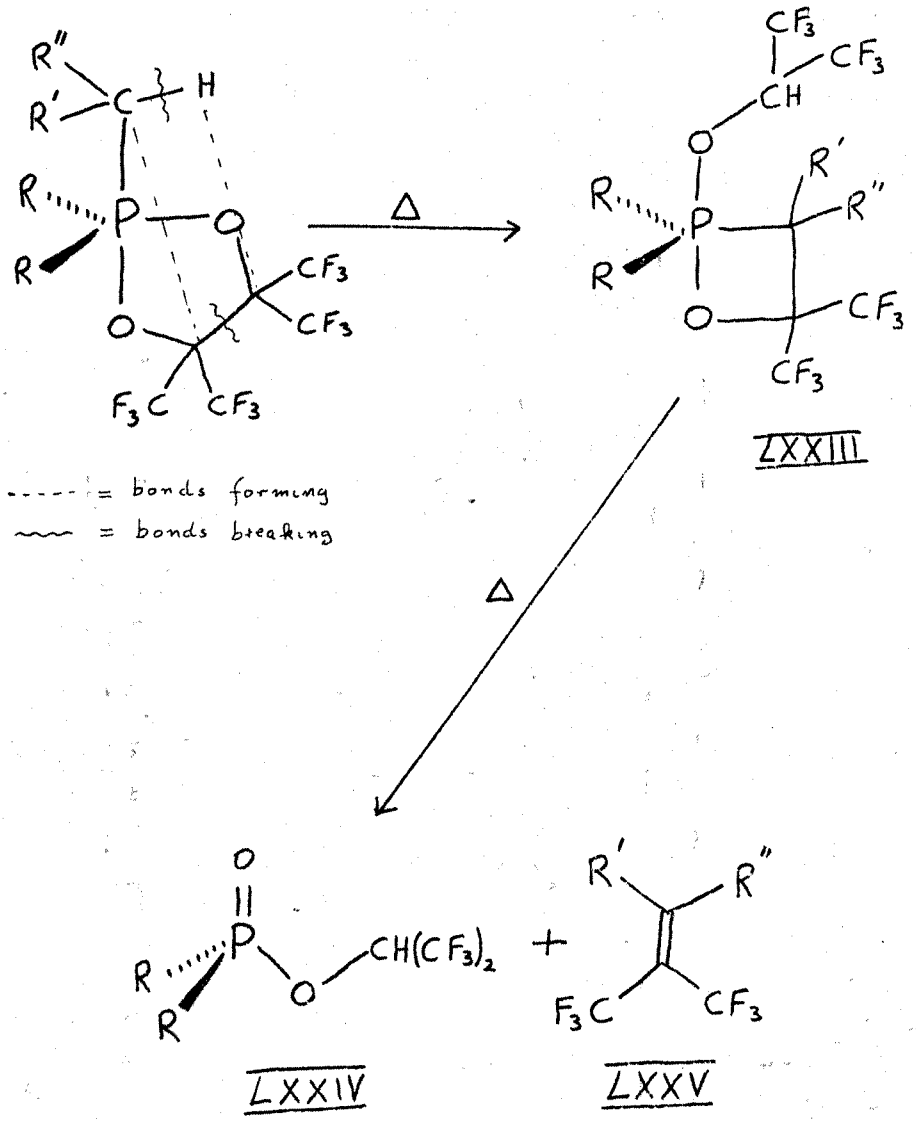


1,4,2- ⟶ 1,3,2-dioxaphospholane



MOLOZONIDE ⟶ "TRUE OZONIDE"

FIGURE XXV

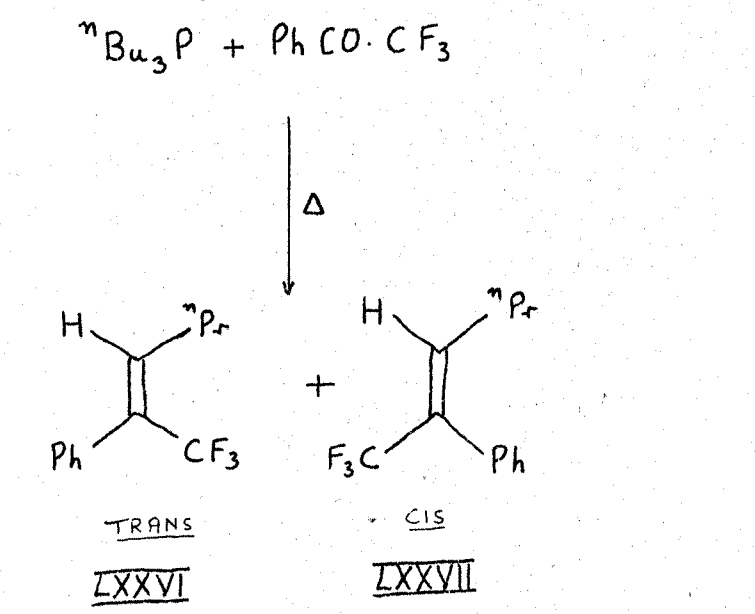


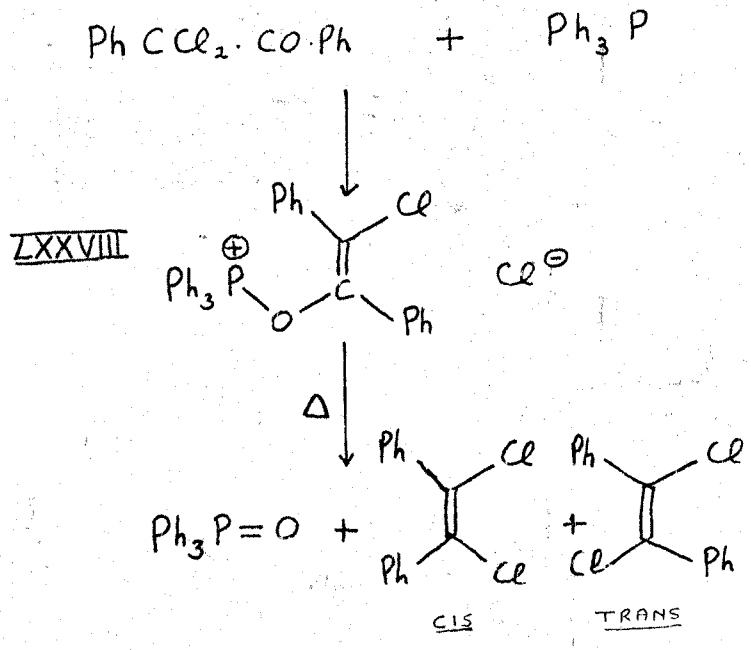
LXXIII

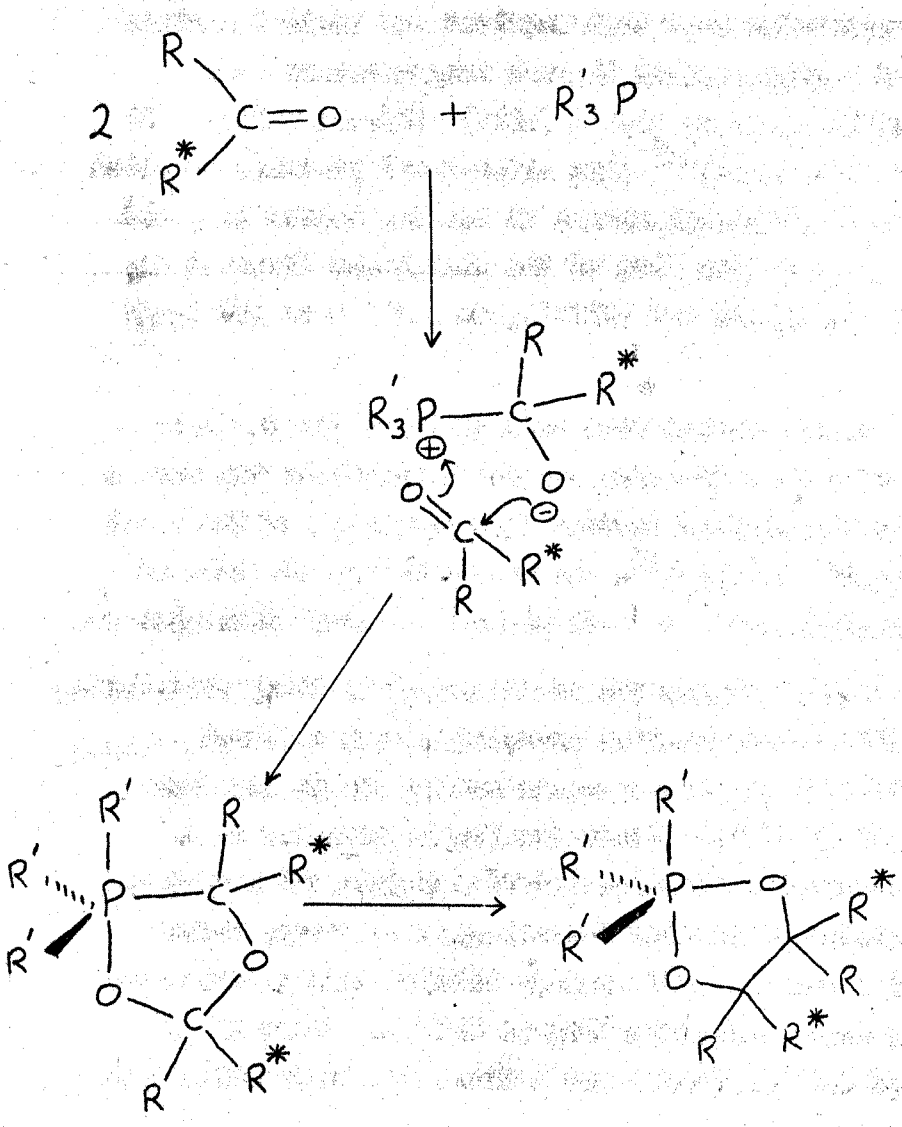
LXXIV

LXXV

FIGURE XXVI


$^nBu_3P$ + $PhCO\cdot CF_3$
Δ
H
^nPr
Ph
CF_3
+
H
^nPr
F_3C
Ph
TRANS
CIS
LXXVI
LXXVII


$PhCCl_2\cdot CO\cdot Ph$ + Ph_3P
LXXVIII
Ph
Cl
$Ph_3P^{\oplus}$
O
C
Ph
$Cl^{\ominus}$
Δ
$Ph_3P=O$ +
Ph
Cl
Ph
Cl
+
Ph
Cl
Cl
Ph
CIS
TRANS



"RAMIREZ" REACTION: R^* = ELECTRON-WITHDRAWING GROUP.

PERKOW REACTION: R^* = GROUP BEARING A HALOGEN ATOM. (Cl, Br, I)

FIGURE XXVII

At higher temperatures than that required for their formation they underwent a quantitative thermal fragmentation to a phosphinate (LXXIV) and an olefin (LXXV) (Figure XXVI). It had previously been shown[143] that tri-n-butyl phosphine reacted with trifluoromethyl phenyl ketone in boiling hexane to yield two isomeric olefins (the fate of the phosphorus fragment was not ascertained), (LXXVI and LXXVII), in a ratio of 3:1 (cis: trans).

It is of some interest that this ratio of 3:1 in favour of the sterically less favoured isomer is precisely the same as that found for the olefins derived from pyrolysis of the "enol phosphonium salt" (LXXVIII)[93], obtained from the reaction of triphenyl phosphine with $\alpha:\alpha$-dichloro-α-phenyl acetophenone.

The similarity between the reactions of tertiary phosphines, triaminophosphines and trialkyl phosphites with carbonyl functions activated by electron-withdrawing groups has been discussed by Ramirez[136]. Since the Perkow reaction is a reaction between a tervalent phosphorus species and a carbonyl compound activated by an electron-withdrawing group, there is clearly at least a formal analogy between this reaction and the reactions discussed above (Figure XXVII). Some of the work described in this thesis was carried out in an attempt to underline this analogy.

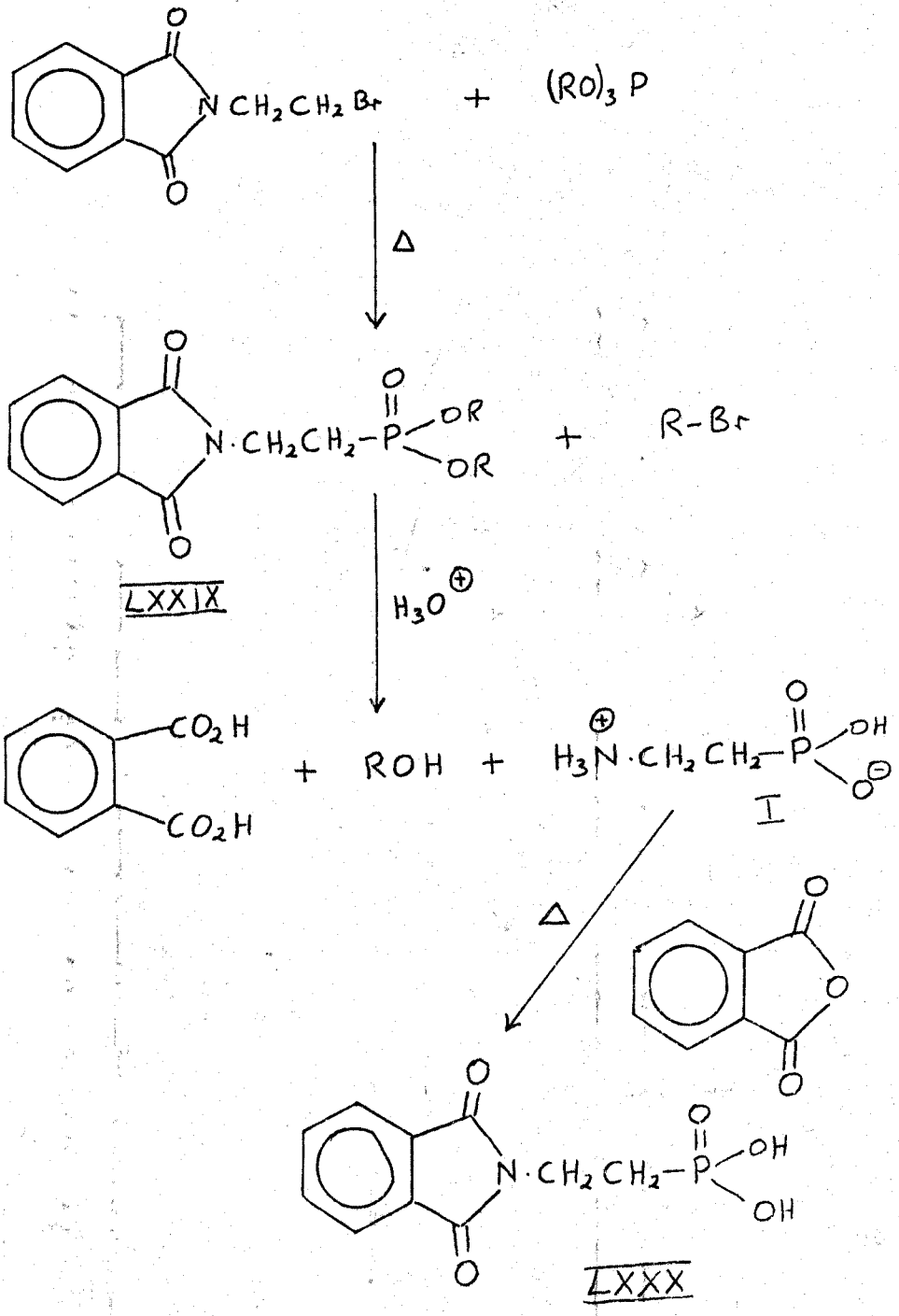


FIGURE XXVIII

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

Synthesis of AEP

In our hands the standard procedures for the synthesis of AEP[49,53,54] led to low yields of impure material. A study of the Kosolapoff[53] procedure was undertaken in an effort to identify the stage at which the greatest loss of material occurred. (Figure XXVIII). The reaction between triethyl phosphite and N—(2-bromoethyl) phthalimide led to an almost quantitative yield of ethyl bromide and a thick brown oil, presumably (LXXIX; R=Et), which could be neither distilled nor crystallised. Hydrolysis of (LXXIX; R=Et) with strong acid yielded a nearly quantitative amount of phthalic acid and a residual brown oil which, chromatographically, contained several phosphorus containing components as well as AEP. Purification of this oil proved very difficult - the best results being obtained by ion-exchange chromatography on Dowex 50 (H^+).

In view of these difficulties, we synthesised N-phthalyl AEP (LXXX) in high yield by condensing AEP with phthalic anhydride. Hydrolysis of this material with strong acid gave AEP as the only phosphorus containing species and a quantitative yield of phthalic acid. Thus, the only stage at which side reactions could be supervening to cause a large reduction in yield appeared to be in the formation of the diester (LXXIX; R=Et). Nucleophilic attack of a trialkyl phosphite at an amide carbonyl function is known[146] but this reaction generally occurs with strongly activated amides, e.g. trihaloacetamides. Ramirez has shown[144,145] that phthalic anhydrides react with triethyl phosphite at elevated temperatures to yield biphthalyls. (Figure XXIX). It is possible that a reaction of this type

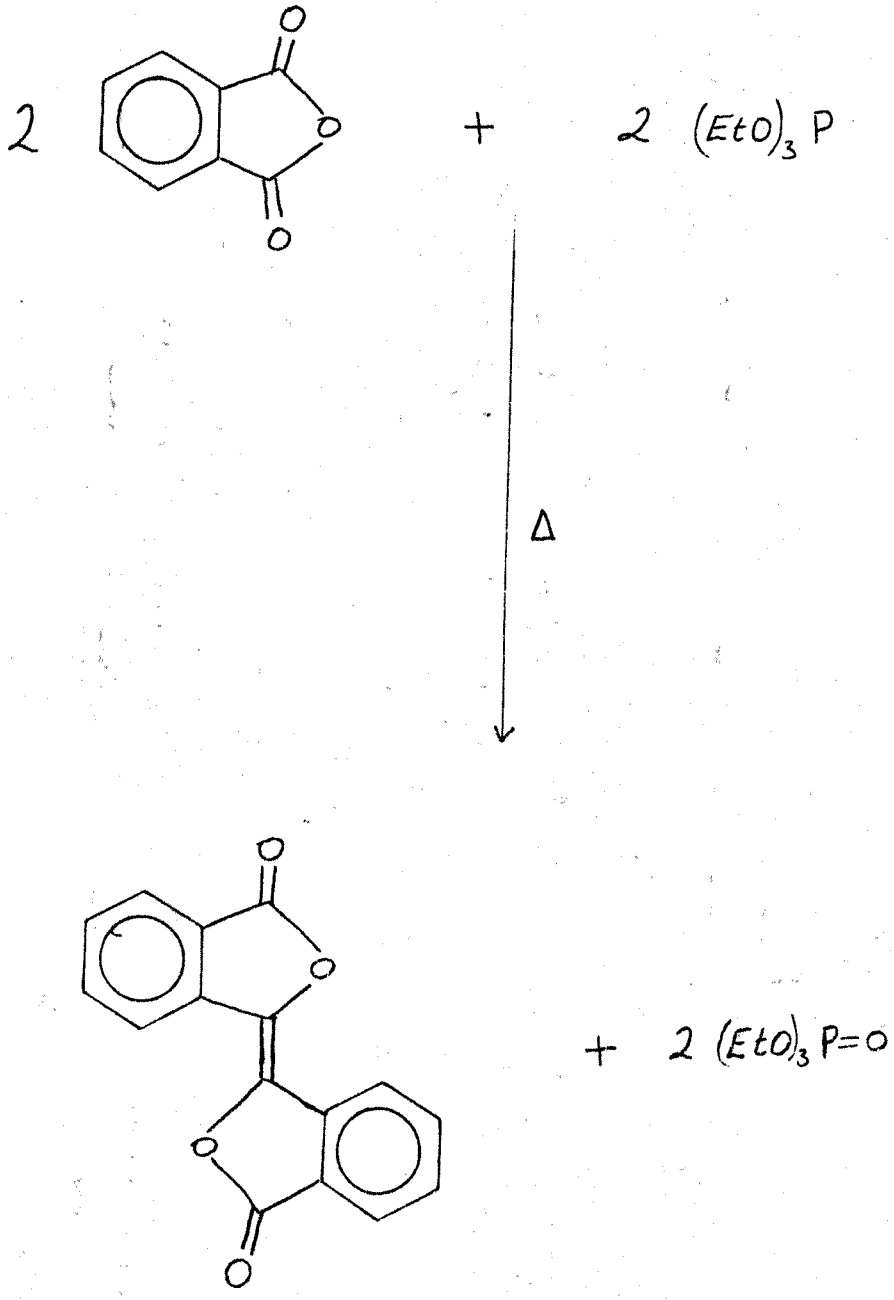


FIGURE XXIX

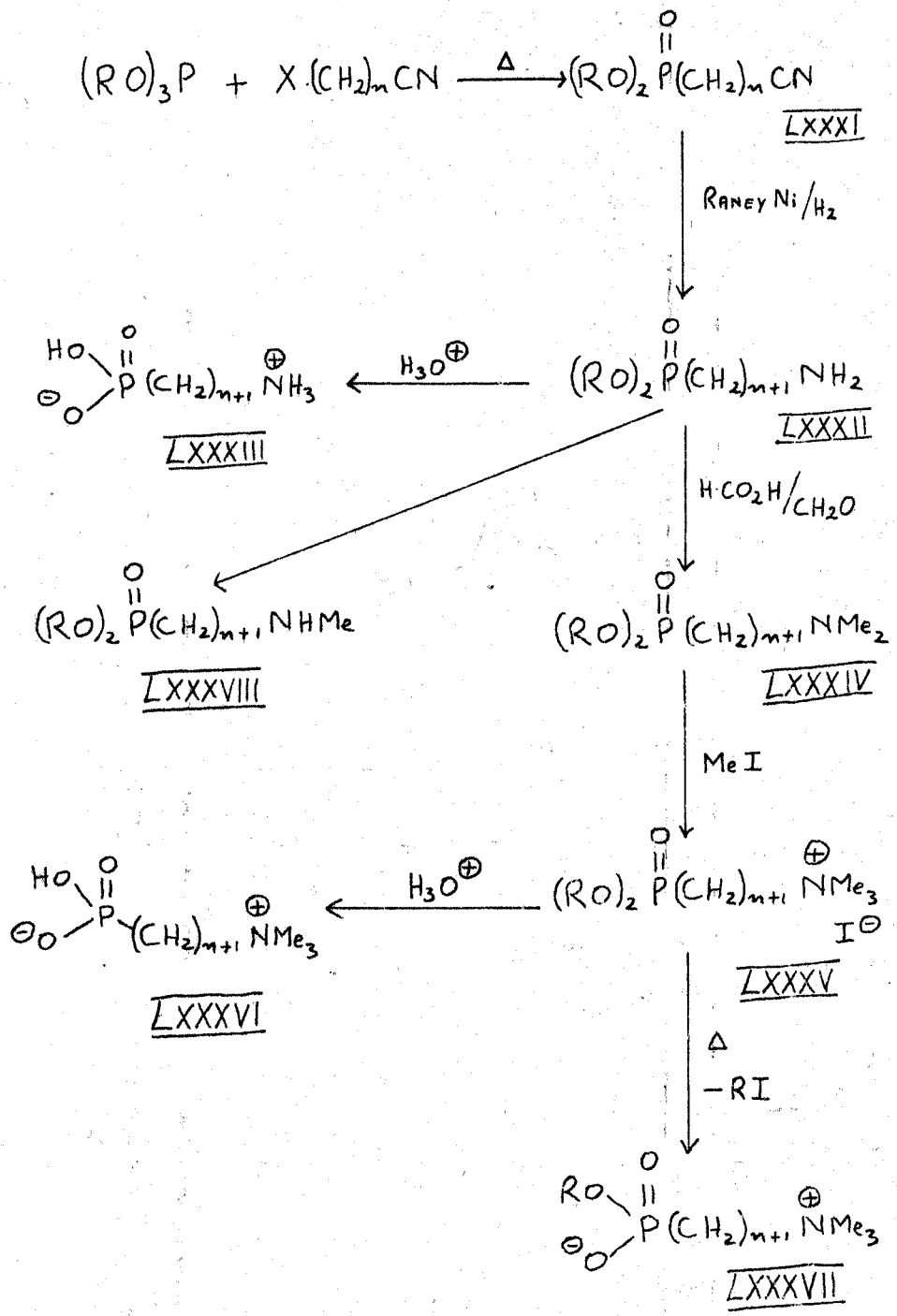

(RO)3P + X(CH2)mCN
Δ
(RO)2P(CH2)mCN
LXXXI
Raney Ni/H2
(RO)2P(CH2)m+1NH2
LXXXII
H3O⊕
HO
O⊖
P(CH2)m+1NH3⊕
LXXXIII
H·CO2H/CH2O
(RO)2P(CH2)m+1NHMe
LXXXVIII
(RO)2P(CH2)m+1NMe2
LXXXIV
MeI
(RO)2P(CH2)m+1NMe3⊕ I⊖
LXXXV
H3O⊕
HO
O⊖
P(CH2)m+1NMe3⊕
LXXXVI
Δ
-RI
RO
O⊖
P(CH2)m+1NMe3⊕
LXXXVII

FIGURE XXX

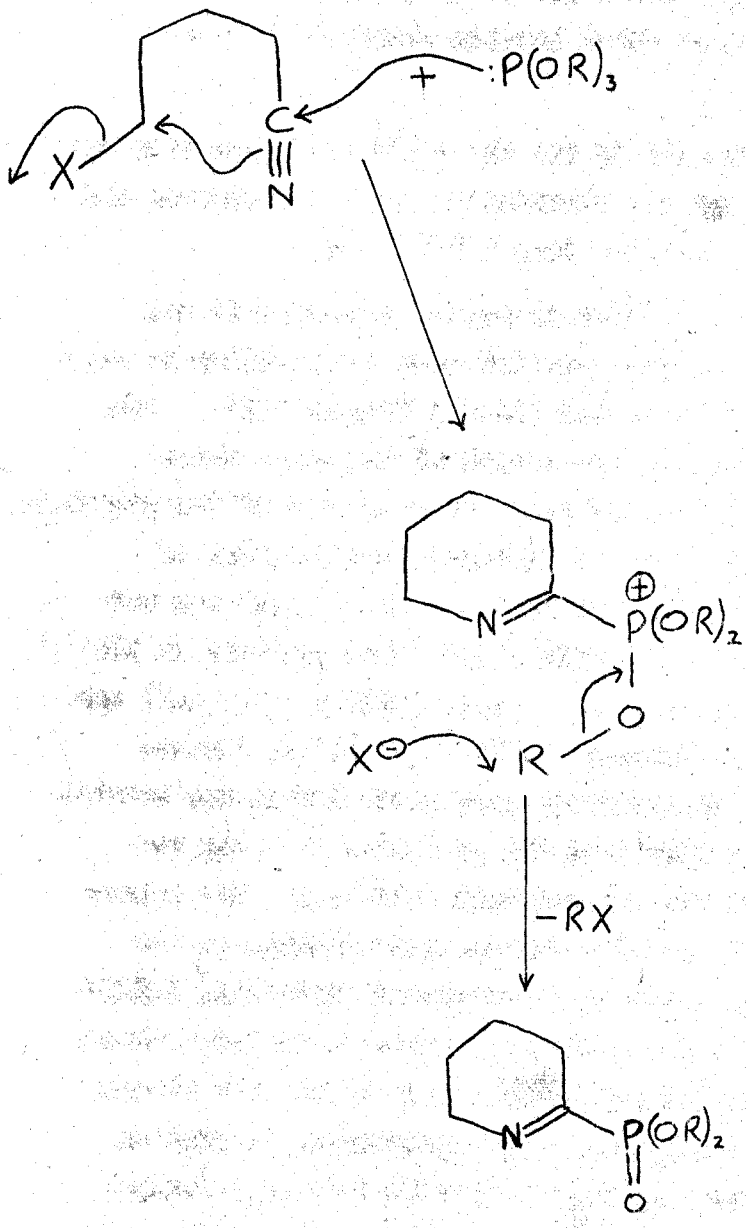


FIGURE XXXI

(between triethyl phosphite and a phthalimide as opposed to a phthalic anhydride) might occur but if so it is difficult to explain the high yields of ethyl bromide obtained in these reactions.

Attempts to prepare AEP by the Chavane[49] procedure likewise proved unfruitful, though the reaction was somewhat cleaner and purification of the product was less troublesome.

In a search for an improved synthetic procedure it was found that trialkyl phosphites reacted with halonitriles to give high yields of ω-cyanophosphonates (LXXXI) (Figure XXX). The yields tended to decrease as the length of the alkyl chain increased, a result which could arise by an attack of the phosphite at the nitrile carbon followed by internal displacement of halogen and dealkylation (Figure XXXI). This result was not studied in detail since acceptable yields were obtained in the cases of diethyl cyanomethyl phosphonate (LXXXI; R=Et, n=1) and diethyl cyano-ethyl phosphonate (LXXXI; R=Et, n=2). Hydrogenation of the cyano phosphonates over Raney Nickel was carried out in a high pressure autoclave and proceeded smoothly to produce high yields of the amino-esters (LXXXII). The amino-esters could be hydrolysed with strong acid directly to the amino-acids (LXXXIII), mono- or dimethylated (LXXXVIII, LXXXIV) or converted, via the N,N-dimethyl derivatives, to the methiodides (LXXXV) which themselves could be hydrolysed with strong acid to the betaines (LXXXVI). The methiodides, on heating above the melting point, readily lost ethyl iodide, a dealkylation which has been observed[207] in related systems (the hydrochlorides of amine phosphonates) and also finds precedent in the work of Clark and Todd[208] who studied the debenzylation

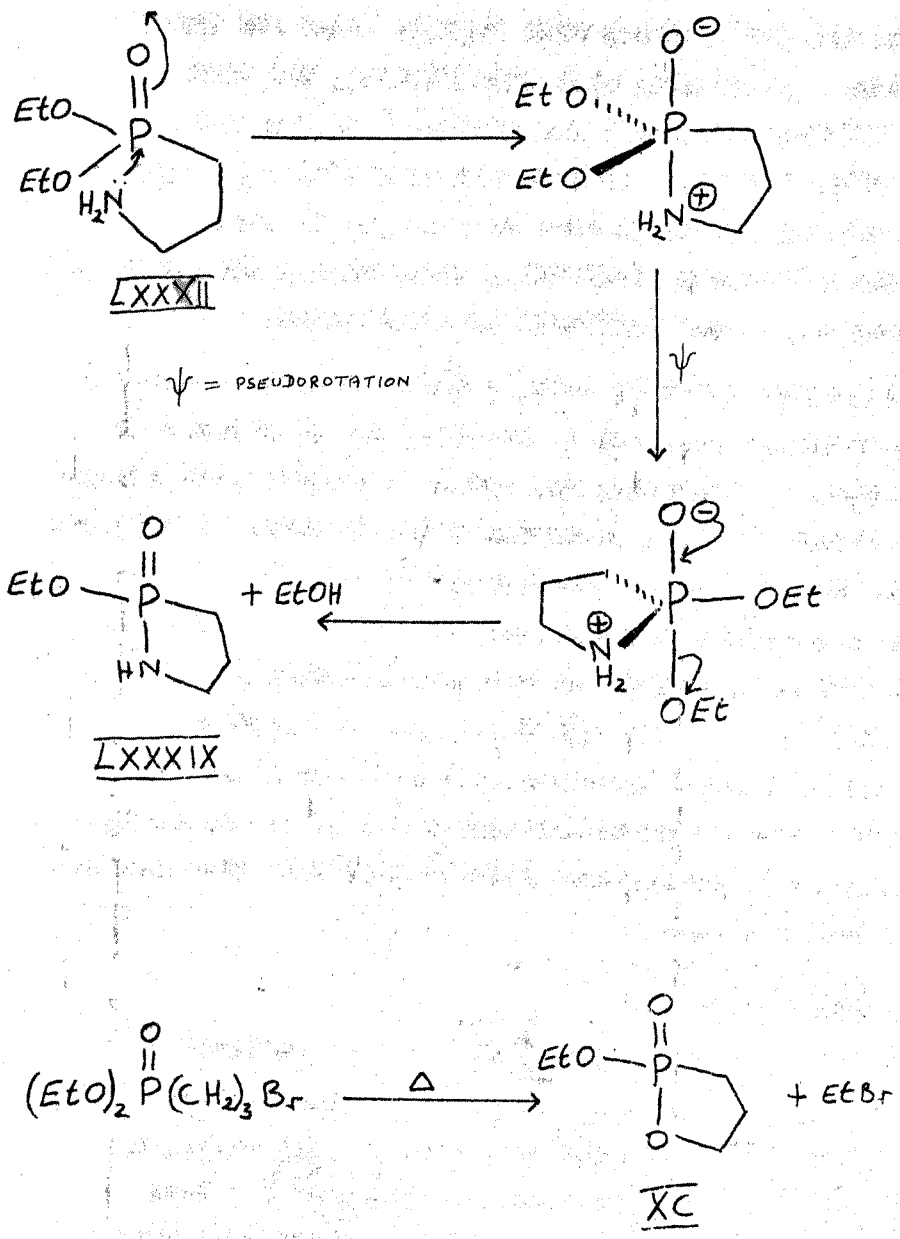


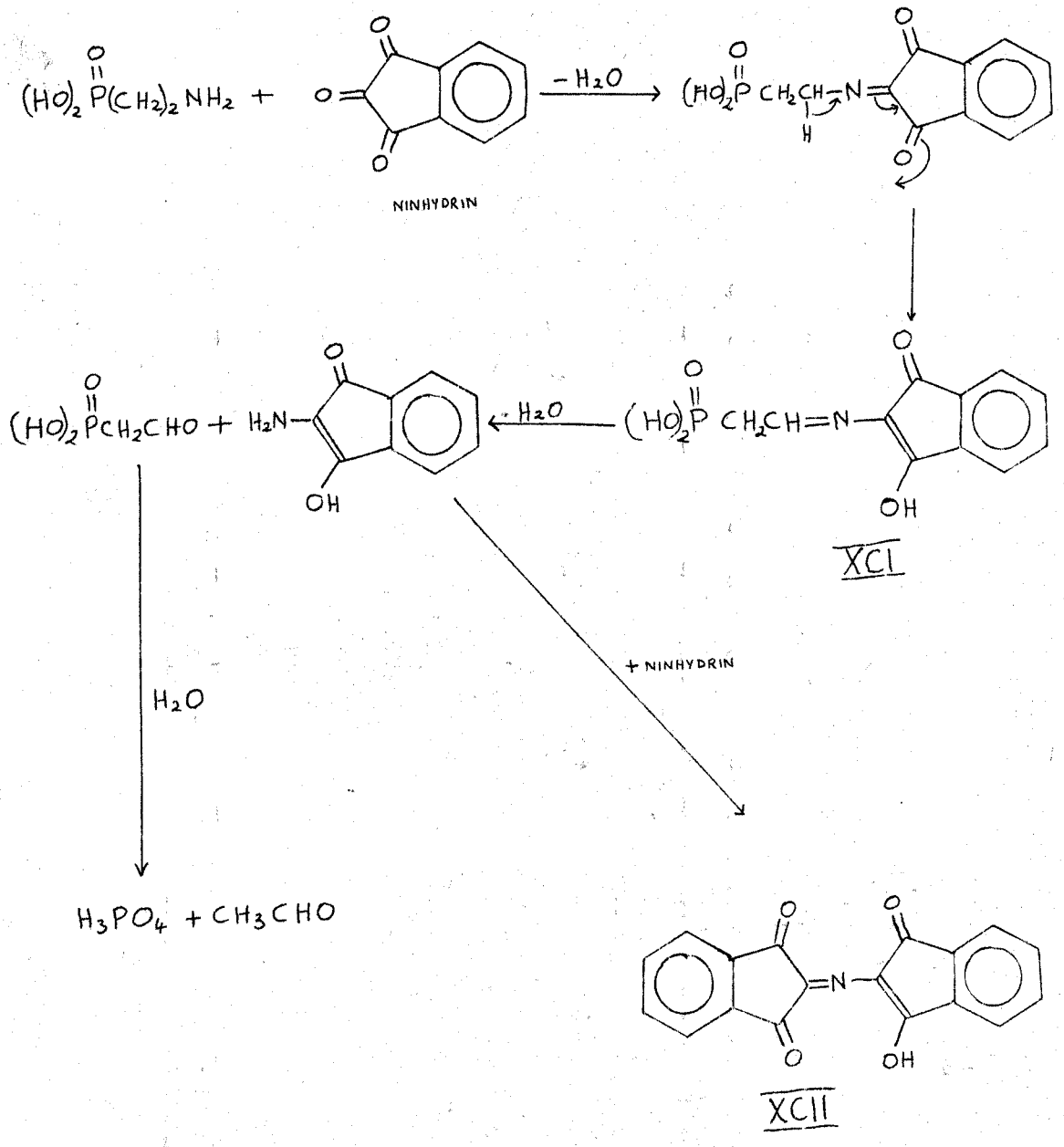
FIGURE XXXII

of phosphates and phosphonates with organic bases and their hydrochlorides. In keeping with this finding, the mass spectrum of (LXXXV; R=Et, n=2) was identical to the mass spectrum of ethyl iodide. Heating the methiodides *in vacuo* above their melting points yielded hygroscopic froths, presumably the half-esters (LXXXVII), which though chromatographically homogeneous, proved difficult to crystallise.

The amino-ester (LXXXII; R=Et, n=2) was found to undergo an internal displacement reaction on standing for some weeks at room temperature. Presumably the internal displacement occurs as shown in Figure (XXXII), involving a pentacovalent phosphorus intermediate which undergoes pseudorotation and elimination. The product, a crystalline solid, was shown to be the cyclic ester amide (LXXXIX), a nitrogen analogue of ethyl propyl phostonate (XC)[147,148]. Though there was some evidence (precipitation of a small quantity of colourless solid on standing) for a similar intramolecular reaction occurring in diethyl 2-aminoethyl phosphonate (LXXXII; R=Et n=1) this product was not examined further.

Activation of AEP

The phosphorus-carbon bond in AEP is very resistant to cleavage by acids and bases[7]. However, AEP reacts with ninhydrin under relatively mild conditions, being degraded thereby to orthophosphate (Pi) and acetaldehyde[50]. This degradation is paralleled *in vivo*, the phosphorus once again appearing as Pi[48]. The reaction of AEP with ninhydrin is believed[50] to follow the course outlined in Figure (XXXIII). An alternative interpretation of the mode of breakdown of (XCI) can be advanced (Figure XXXIV). This is based on the



XCII IS RESPONSIBLE FOR THE PURPLE COLOURATION IN REACTIONS OF NINHYDRIN WITH AMINO-ACIDS

FIGURE XXXIII

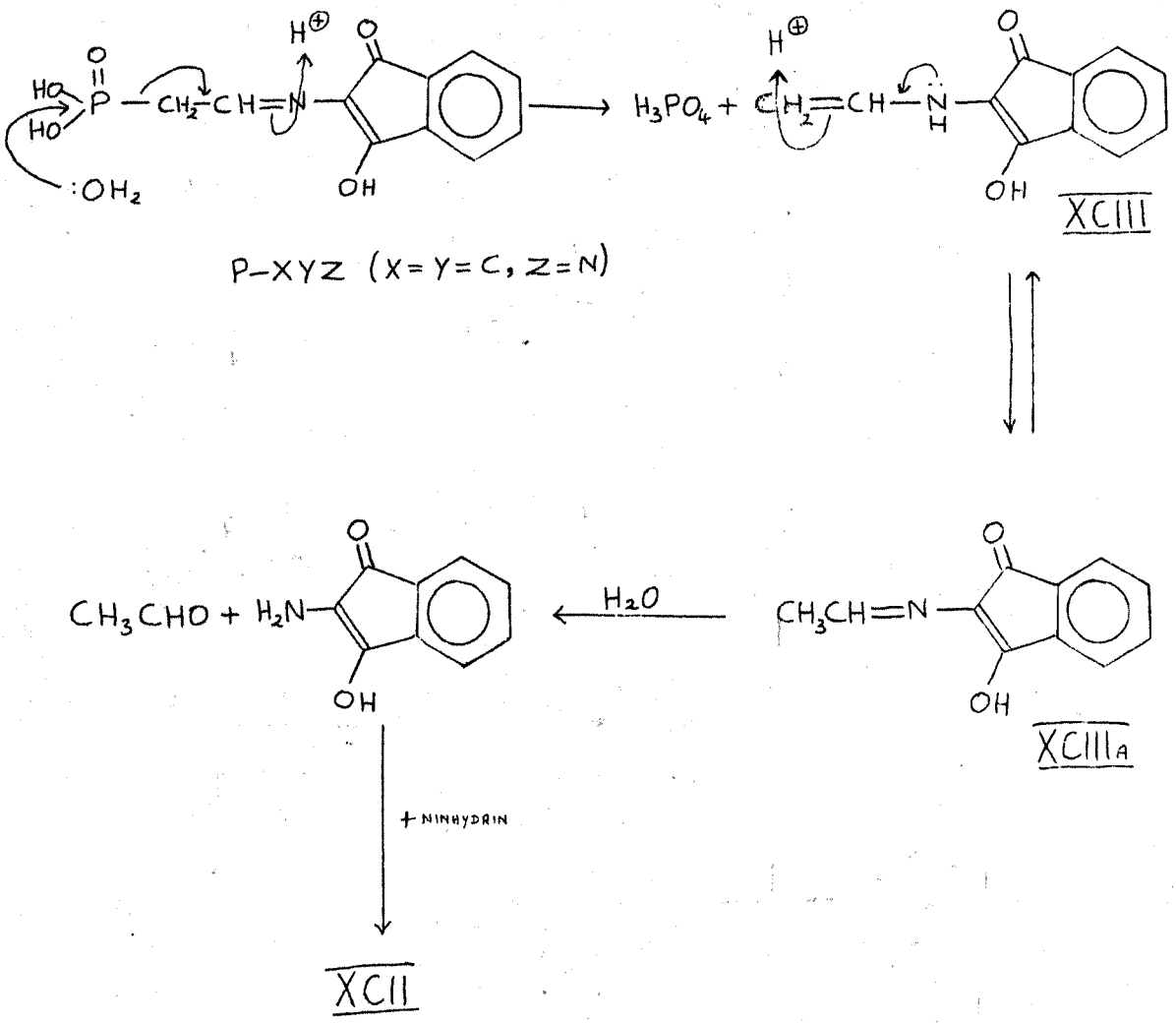
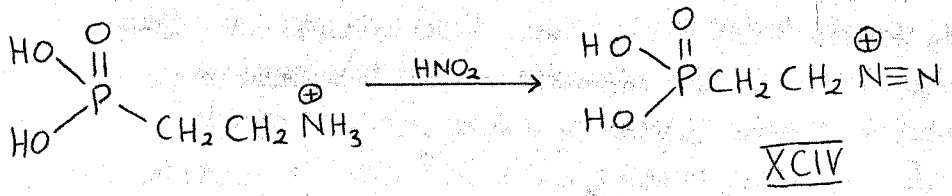
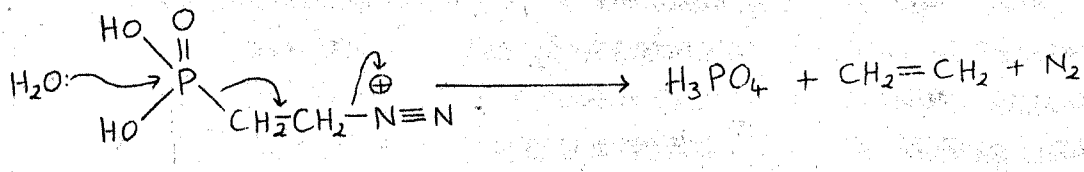


FIGURE XXXIV

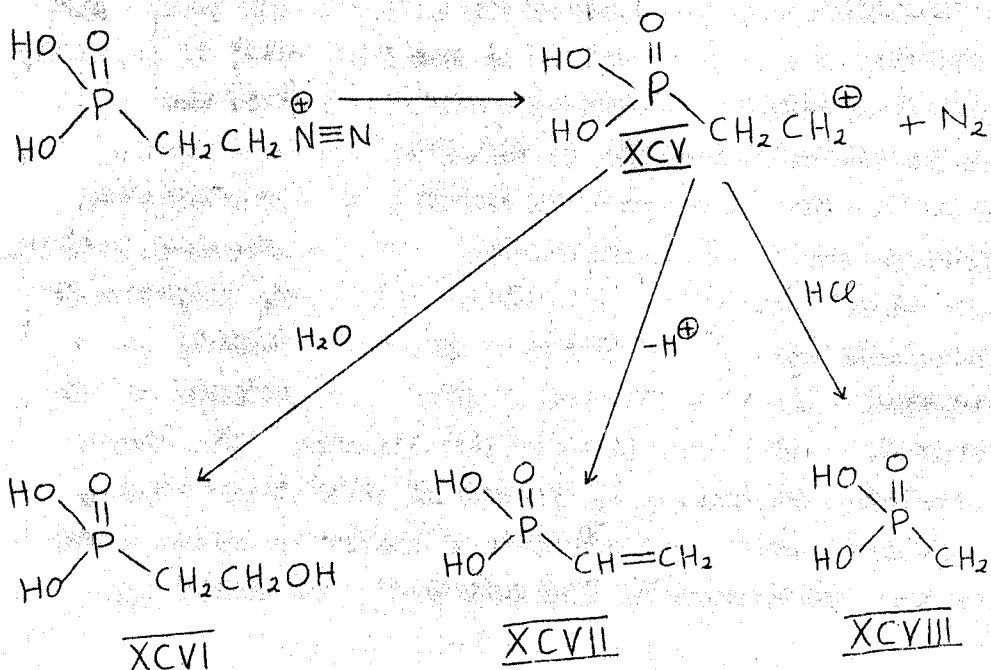


XCIV

(i)



(ii)



XCV

XCVI

XCVII

XCVIII

FIGURE XXXV

rationale proposed by Clark and Hutchinson[52] for phosphoryl transfer, namely P-XYZ activation. This alternative scheme could help to explain the observation that inorganic phosphate is produced at a rate (pseudo $k_1 = 4.6 \pm 0.7 \times 10^{-3}$ min.$^{-1}$) greater than the rate ($k = 4.0 \pm 1.5 \times 10^{-3}$ min.$^{-1}$) of production of the ninhydrin colour. The enamine (XCIII) would be expected to be in equilibrium with its tautomer (XCIIIa), the equilibrium being shifted in favour of the latter by its reaction with water.

In an attempt to activate AEP by a similar procedure, we diazotised it in acidic aqueous solution. The two most reasonable reaction routes are outlined in Figure (XXXV). The initial product of diazotisation was expected to be the diazonium compound (XCIV)[149]. If (XCIV) were to undergo P-XYZ displacement the products would be orthophosphoric acid, ethylene and nitrogen. The alternative decomposition route involving the fragmentation or reaction of the carbonium ion (XCV) might be expected to lead to a variety of products (XCVI) to (XCVIII). In practice, only one phosphorus containing product was observed chromatographically in the diazotisation mixture. This product was shown not to be (XCVIII) by chromatographic comparison with an authentic sample. The diazotisation product, though stable indefinitely in solution below pH2, underwent an increasingly rapid decomposition as the pH was raised, the decomposition becoming vigorous at pH7. Two products of this decomposition were found to be Pi and ethylene. The latter was confirmed by sweeping N_2 through the mixture and passing the effluent gases into a solution of bromine in carbon tetrachloride. Examination of this solution by GLC showed 1,2-

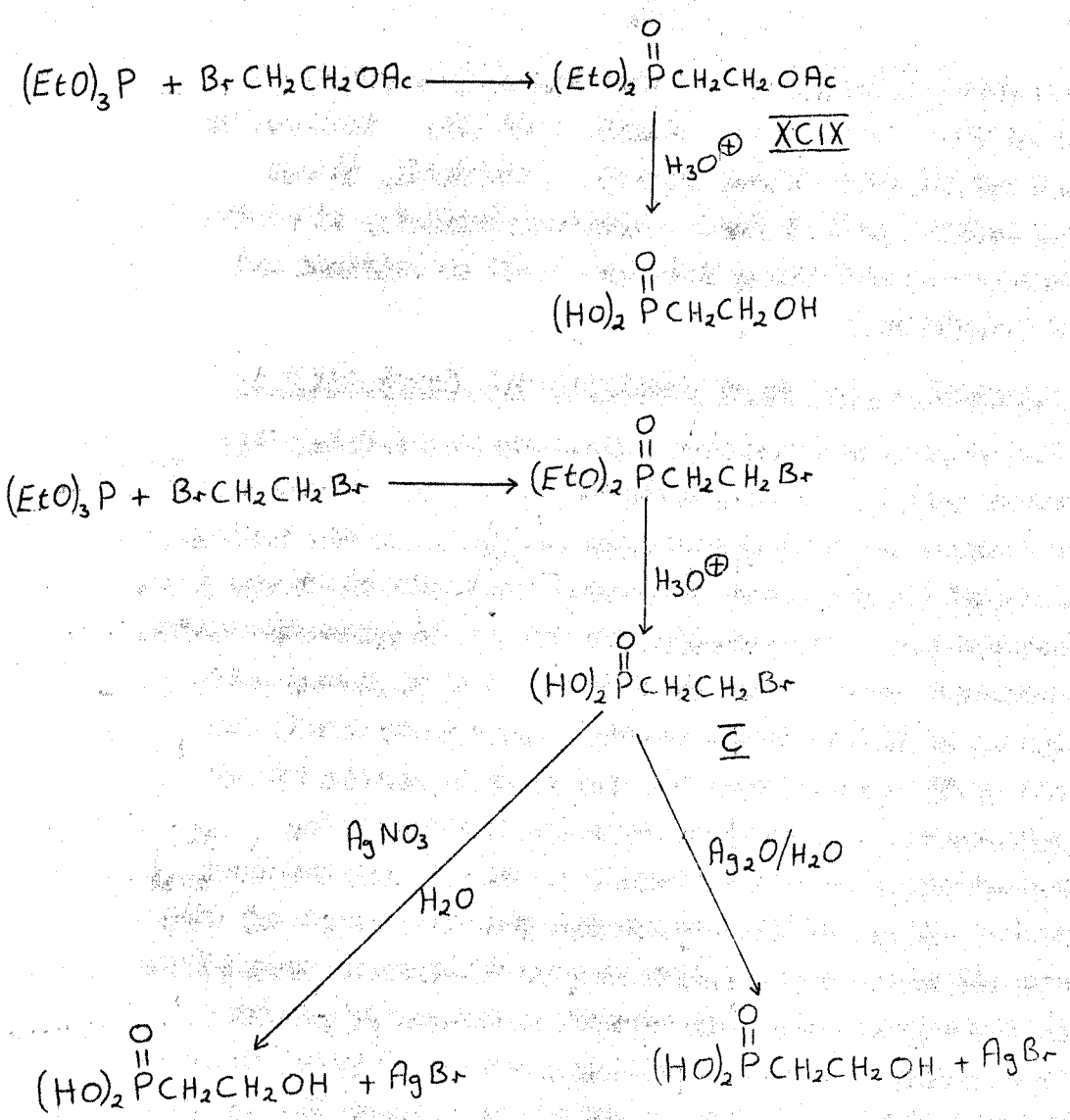


FIGURE XXXVI

dibromoethane to be present. This observation pointed to (XCVI) as the product of diazotisation of AEP. Attempts to isolate the material proved uniformly unfruitful, though aqueous acidic (pH 2 or less) solutions containing it as the only phosphorus containing component could be obtained and stored indefinitely.

Attempted syntheses of 2-hydroxyethyl phosphonic acid

Whilst several literature references to 2-hydroxyethyl phosphonic acid (XCVI) or its diethyl ester were in existence[214-216], without exception these either gave no details of the material or mentioned its isolation as a heavy metal salt which could not be characterised. Accordingly, we set out to synthesise (XCVI) by a rational route (Figure XXXVI). Whilst strong acid hydrolysis of diethyl 2-acetoxyethyl phosphonate (XCIX) led to some of the desired product, the reaction mixture showed, chromatographically, a number of phosphorus containing components and it proved impossible to isolate the required material. Treatment of 2-bromoethyl phosphonic acid (C) with aqueous silver nitrate solution at room temperature resulted in the appearance of one new phosphorus containing component. The same material resulted from treatment of (C) with silver oxide in water at 50°C. Using the silver nitrate procedure, a solution (obtained after removal of the theoretical amount of Ag Br) revealing only one phosphorus containing species (chromatographically) was obtained. Efforts to isolate this species proved unsuccessful, decomposition to ethylene (confirmed by conversion to 1,2-dibromoethane) and Pi always occurring. The species in solution was found to migrate, chromatographically, at the same rate as the AEP diazotisation

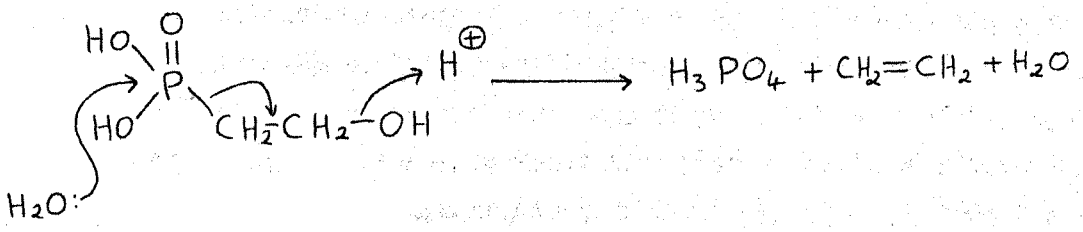


FIGURE XXXVII

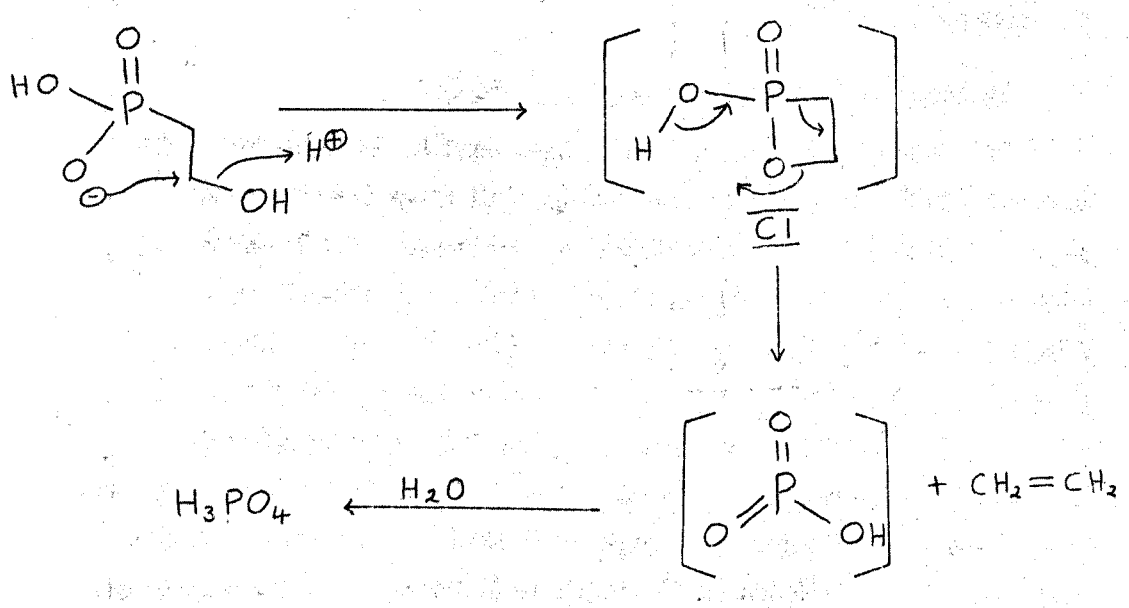


FIGURE XXXVIII

product. These observations, coupled with the methods of synthesis of (XCVI), seemed fairly sure indications that diazotisation of AEP in aqueous solution led to 2-hydroxyethyl phosphonic acid (XCVI) and that therefore the normal S_N1 reaction of alkyl diazonium cations with water had supervened over a potential P-XYZ fragmentation.

Diazotisation of 3-aminopropylphosphonic acid

Diazotisation of the next highest homologue of AEP, 3-aminopropylphosphonic acid, led once again to a single new phosphorus containing component. By comparison with an authentic sample, this material was shown to be 3-hydroxypropyl phosphonic acid. In this case, isolation proved relatively easy and the product showed no inclination to decompose. This result was to be expected in view of the known behaviour of 3-hydroxypropyl phosphonic acid[147].

Mechanism of fragmentation of (XCVI)

The observation that (XCVI) was stable in acid solution but unstable in neutral or alkaline solution seems rather surprising for such a compound, as written. Protonation of the alcoholic oxygen might be expected to facilitate the departure of the hydroxyl group as H_2O, in a P-XYZ type of displacement (Figure XXXVII). Alternatively, internal displacement of the hydroxyl group by the phosphonic acid anion might be envisaged (Figure XXXVIII) and although increasing the pH would tend to favour the ionisation of the acid function, the tendency of the hydroxyl group to leave would be correspondingly reduced. Whilst the above decomposition routes are thus unlikely, the latter is suggestive of an intermediate (CI) which could well exhibit the properties we have observed.

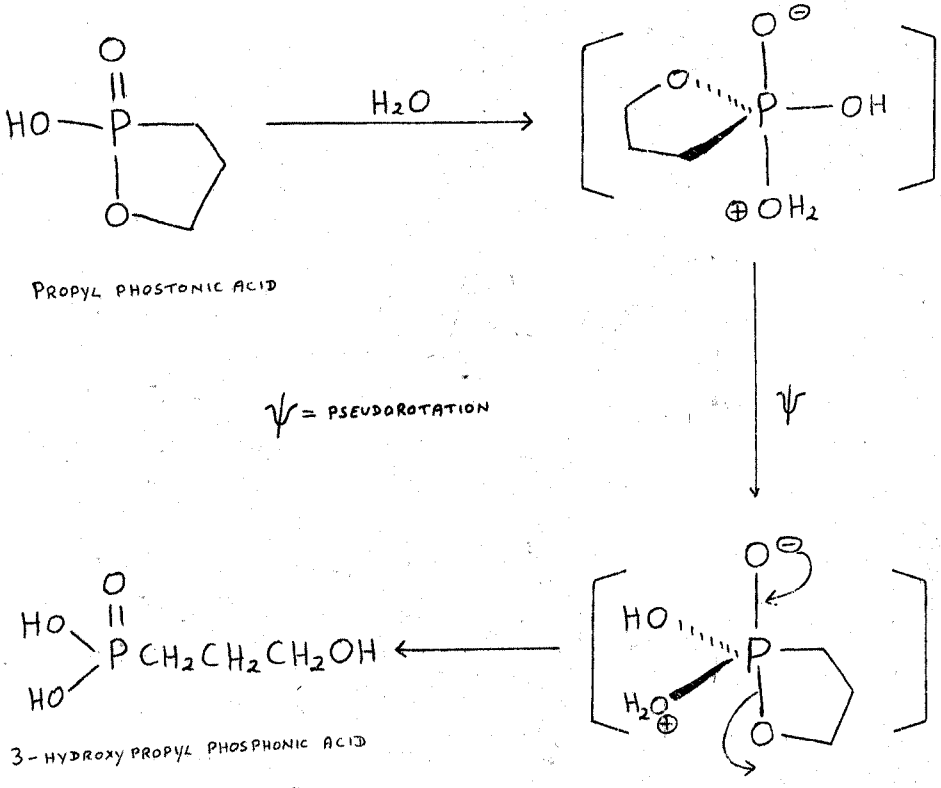


FIGURE XXXIX

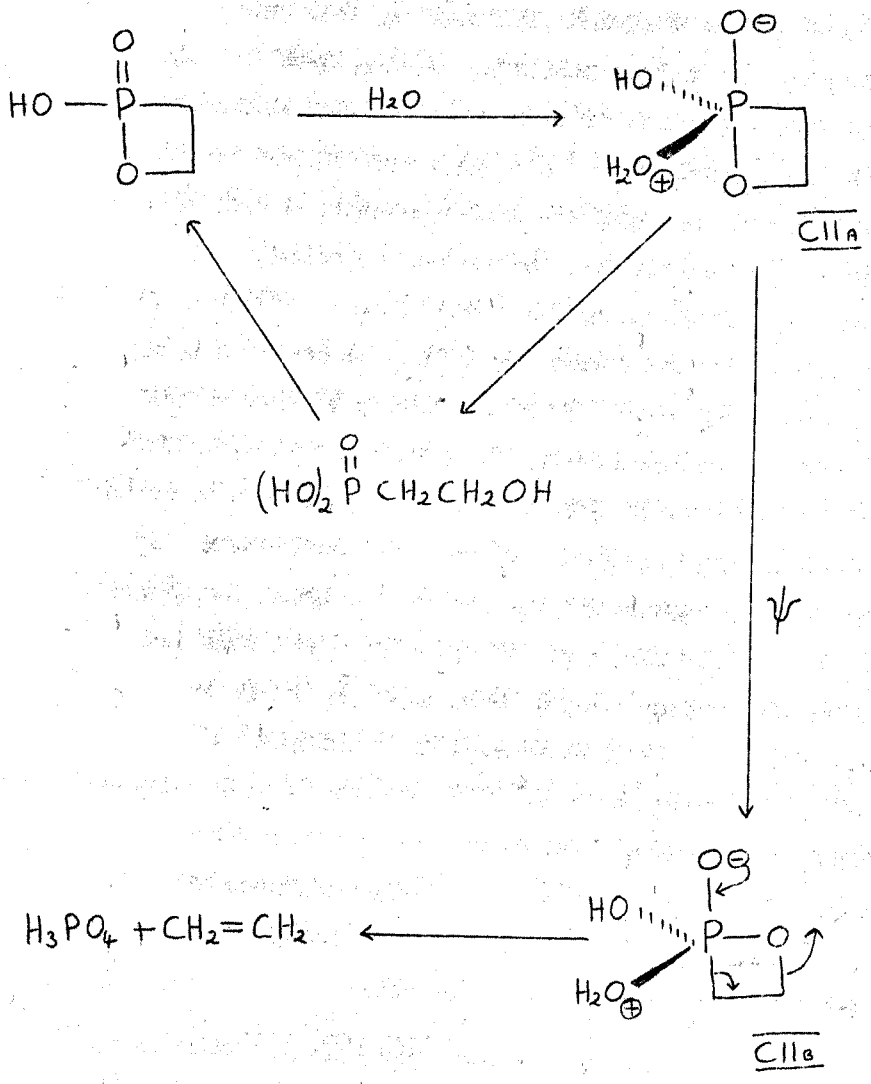


FIGURE XL

Westheimer has shown[147] that 5-membered ring phostonates are hydrolysed at a rate some 10^5 to 10^6 greater than the corresponding open chain phosphonates. Furthermore, it was shown that this hydrolysis proceeds entirely by P-O bond fission, whereas open chain phosphonates, during hydrolysis, underwent roughly equal amounts of P-O and C-O bond cleavage. Subsequent studies have indicated that this hydrolysis proceeds by way of a pentacovalent phosphorus intermediate, a molecule of water being co-ordinated as the first step, followed by pseudorotation and apical elimination (see Figure XXXIX). A four-membered ring phostonate (e.g. CI) would be expected, if formed, to be considerably more reactive than a five-membered homologue. If such an intermediate were formed and underwent solvation to the pentacovalent intermediate (CII), pseudorotation would lead to different proportions of the two conformers (a) and (b) (Figure XL). Conformer (a) could decompose as shown to the starting open chain phosphonate whereas conformer (b) (an unfavourable conformation) might decompose as shown to produce ethylene and Pi. Such a solvated, pentacovalent intermediate would be expected to be more stable at low than at high pH, increase of pH leading to dissociation of a P-OH function and subsequent decomposition. Decomposition of conformer (a) is obviously reversible via the cycle shown, whereas that of conformer (b) is irreversible.

The above may be the explanation of the observations made but until the hydroxyacid (XCVI) itself can be isolated and its behaviour studied, this must remain speculative.

ENOL PHOSPHATE REARRANGEMENTS

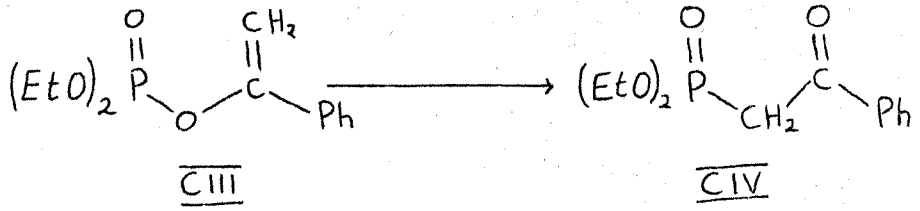
The rearrangement of enol benzoates and acetates to the corresponding β-dicarbonyl compounds has been shown to occur thermally[150], photochemically[152,153] or under the influence of Lewis acids[150,151]. A simple calculation of the free energy change involved in such a rearrangement can be made from the bond dissociation energies of the reactant and product molecules. Thus for a rearrangement C-X-Y=Z $\longrightarrow$ C-Z-Y=X, the value $\triangle$, where $\triangle$ is defined as:-

$$\triangle = [D(C-Z) + D(Z-Y) + D(Y=X)] - [D(C-X) + D(X-Y) + D(Y=Z)]$$

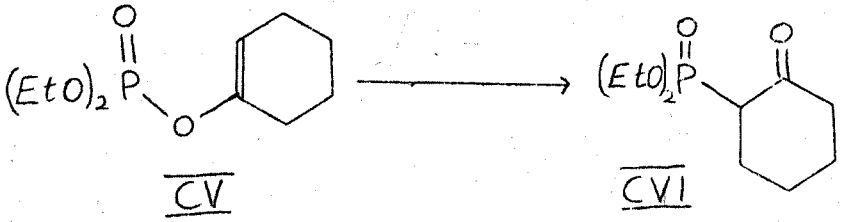
provides a rough guide to the energy requirements of the rearrangement. Table II, embodying the figures obtained in a series of such calculations has already been presented, from which it can be seen that the rearrangement of enol acylates to β-dicarbonyl compounds is favoured by some 27 kcal.mole^{-1}.

However, such a calculation is at best a very approximate guide to the likelihood of a rearrangement occurring in any given case. Applying this approach to a hypothetical rearrangement of enol phosphates to β-ketophosphonates, a value of $\triangle$ = 8.3 kcal.mole^{-1} is obtained. This would seem to imply that such a rearrangement could be favourable, energetically. Models indicate that such a rearrangement is geometrically feasible. Approach of the terminal carbon (of the double bond function) to the phosphorus to within approximately 2.7Å is possible, based on reasonable estimates of bond lengths and angles[155].

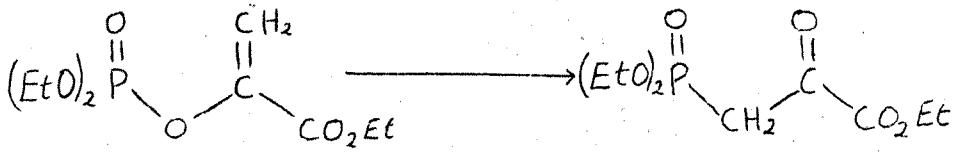
It is well established that the proportions of phosphonate esters and enol phosphate esters formed in the Perkow reaction are dependent upon the temperature at which the reaction is



CIII CIV



CV CVI



CVII CVIII

FIGURE XLI

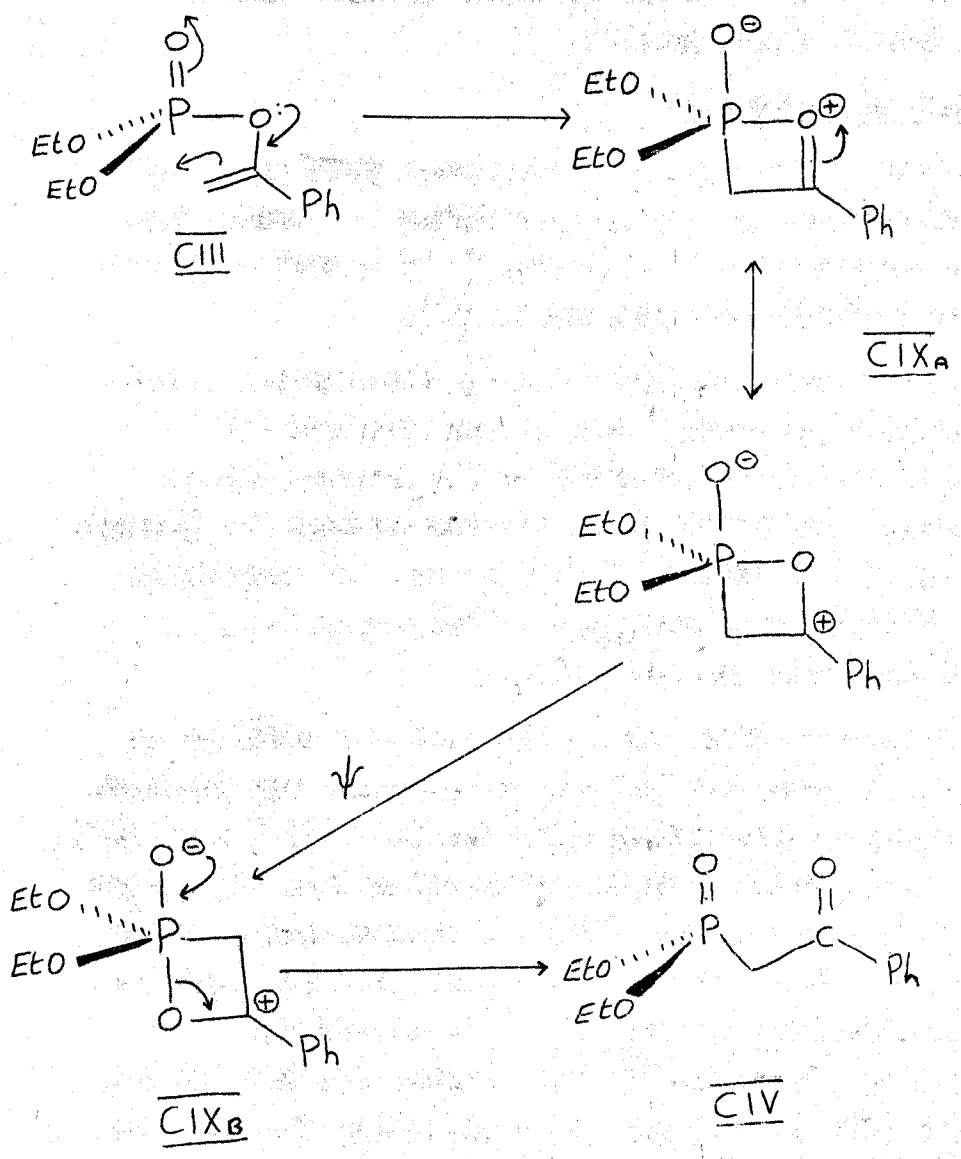


FIGURE XLII

carried out[102]. Accordingly, our first studies concerned thermally induced rearrangements.

Thermal rearrangements

Treatment of pure diethyl 1-phenylvinyl phosphate (CIII) with xylene followed by boiling under reflux for several days led to the appearance of small amounts (< 3% by GLC) of diethyl benzoylmethyl phosphonate (CIV, Figure XLI).

A similar result was obtained using acetic acid as solvent. Similar treatment of diethyl cyclohexenyl phosphate (CV) produced a barely measurable amount of the isomeric diethyl 2-oxocyclohexyl phosphonate (CVI), whereas triethyl PEP (diethyl 1-carbethoxyvinyl phosphate, CVII) under the same conditions, showed no evidence of rearrangement to the isomeric ethyl 3-(diethyl phosphono) pyruvate (CVIII).

The observation that (CIII) rearranged to a small extent to (CIV) seemed explicable in terms of a 4-centre rearrangement passing through an intermediate carbonium ion (CIX) (Figure XLII). Such a carbonium centre would be stabilised by both the adjacent oxygen and the phenyl group. (CIX_A), as an intermediate, could pseudorotate to (CIX_B), which conformation would be expected to be preferred, with the P-O bond of the 4-membered ring occupying an apical position[157,158]. Subsequent decay of this intermediate ($CIX_B \longrightarrow$ CIV, arrows) should follow the route outlined, groups leaving from apical positions representing a lower energy situation[156,157]. Conversely, a carboethoxy group and, to a lesser extent, a cyclohexyl residue, in place of the phenyl group would destabilise an incipient carbonium centre. Furthermore, the cyclohexyl residue would present a geometrical barrier to the formation of an intermediate analogous to (CIX)

since the requirements of the carbonium centre (preferred conformation is planar) would impose a large angle strain on a 4-membered ring fused to a 6-membered ring.

It is of some interest that the (CIII ⟷ CIV) system was studied by Borowitz and his co-workers[73]. Heating a mixture of the two isomers with glacial acetic acid they observed a limiting proportion of 2.75% rearrangement of the β-keto phosphonate to the enol phosphate by NMR measurement of the isomer ratio in the mixture. In order to compare this effect with the effect on a pure enol phosphate, we heated (CIII) in glacial acetic acid and observed the appearance of a small amount (< 5% by GLC) of the isomeric (CIV). In contrast, neither (CV) nor (CVII) showed any evidence of rearrangement under these conditions.

Photochemical rearrangements

Photolysis of dioxan, ethanol, cyclohexane or benzene solutions of (CIII, CV and CVII) failed to result in the appearance of detectable amounts of the isomers (CIV, CVI and CVIII, respectively). The reactions were followed by means of infra-red spectroscopy, the appearance of a carbonyl absorption being taken as a first indication of rearrangement. In practice, ethanol solutions of (CIII) exhibited carbonyl absorption very quickly. Further examination (by GLC) showed this to be due to acetophenone, arising presumably by P-O bond fission and H-abstraction from the solvent. Long irradiation times, particularly in the case of solutions of (CVII), led to the accumulation of an appreciable quantity of polymeric material.

Irradiation, by sunlight, of a sample of (CIII) in the absence of solvent for several weeks was found to result only in some polymerisation, no evidence of rearrangement being detectable by GLC.

Lewis acid catalysed rearrangements

Benzene solutions of (CIII) and (CV), respectively, were stirred at room temperature for several weeks with small amounts of p-toluene-sulphonic acid, boron trifluoride-diethyl etherate and boron trifluoride-acetic acid complex respectively. Some indications of rearrangement were obtained though in no case was the rearrangement appreciable.

A further series of experiments was designed to ascertain whether isomerisation of enol phosphates to β-ketophosphonates occurred under the conditions of the Perkow reaction used to synthesise them. Accordingly, thermal treatment of (CIII) and (CV) in the presence of phenacyl chloride and 2-chlorocyclohexanone, respectively, was investigated. Similarly, irradiation of both compounds in the presence of their respective α-haloketone precursors was examined. The results of these and the previously discussed experiments are collected in Table III.

TABLE III

EXPERIMENT	A^T	B^T	C^P	D^P	E^P	F^L	G^L	$H^{L,T}$	I^L	J^T	K^P
SUBSTRATE											
CIII	-	+	0	+	-	-	-	+	-	+	-
CV	-	+	-	-	-	-	-	-	-	-	-
CVII	-	-	0	-	-	-	-	+?	-	0	0

Notes: (1) Experiments A-J denote the following conditions:- A, Δ, no solvent; B, Δ, xylene; C, $h\nu$, no solvent; D, $h\nu$, cyclohexane; E, $h\nu$, dioxan ethanol;
F, BF_3/AcOH; G, BF_3:OEt_2; H, Δ, AcOH; I, C_6H_6/p-toluene sulphonic acid; J, Δ, α-haloketone; K, $h\nu$, α-haloketone.

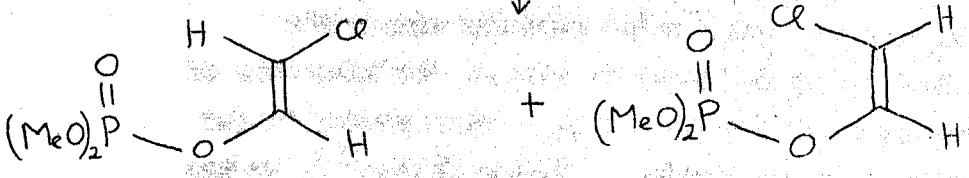
(ii) T = thermal, P = photochemical, L = Lewis acid catalysed

(iii) + = Rearrangement, +? = trace of rearrangement, - = no rearrangement, 0 = experiment not performed.

The results in Table III show that rearrangements of enol phosphates to β-keto-phosphonates can occur under certain conditions, though under the variety of conditions employed, no isolable quantities of the rearrangement products were formed. That such a rearrangement can occur, or perhaps that an equilibrium exists, between enol phosphates and β-ketophosphonates is important, even though, in vitro, such rearrangements occur in very low yields, since, as has been pointed out earlier, a biological system requires only that an equilibrium be set up, one component of which can be removed, thus forcing the reaction to completion.

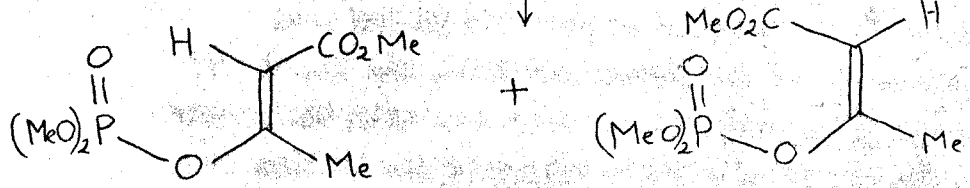
$(MeO)_3P + Cl_2CH.CHO$

Reaction A



TRANS (80%) CIS (20%)

$(MeO)_3P + CH_3CO.CHCl.CO_2Me$



TRANS (67%) CIS (33%)

FIGURE XLIII

THE PERKOW REACTION

The plethora of mechanisms proposed and the amount of experimental data amassed regarding the Perkow reaction render the choice of a suitable approach to the problem a difficult one. Despite this considerable accumulation of data, very few of the experiments have been conducted under strictly comparable conditions, so that it is difficult to compare the behaviour of different α-halocarbonyl compounds with a given phosphite (or vice versa) except by extrapolation. Lichtenthaler[102], in his review, has expressed the conviction that detailed stereochemical studies will "furnish the material to establish with certainty the mechanistic course" of the Perkow reaction. It should, perhaps, be mentioned that this comment was made in connection with an apparently anomalous stereochemical result arising from a Perkow reaction. This result[159] (See figure XLIII) has been misinterpreted by the reviewer, who quotes reaction A as leading to 80% cis, 20% trans product, and is not anomalous.

Nevertheless, this stereochemical point is important, as any acceptable mechanism must needs account for the observation that where geometrical isomerism is possible in the enol phosphates synthesised by the Perkow reaction, the isomer with the larger groups trans predominates over that with the larger groups cis to the extent of a ratio trans:cis rarely less than 3:1[160] and usually greater.

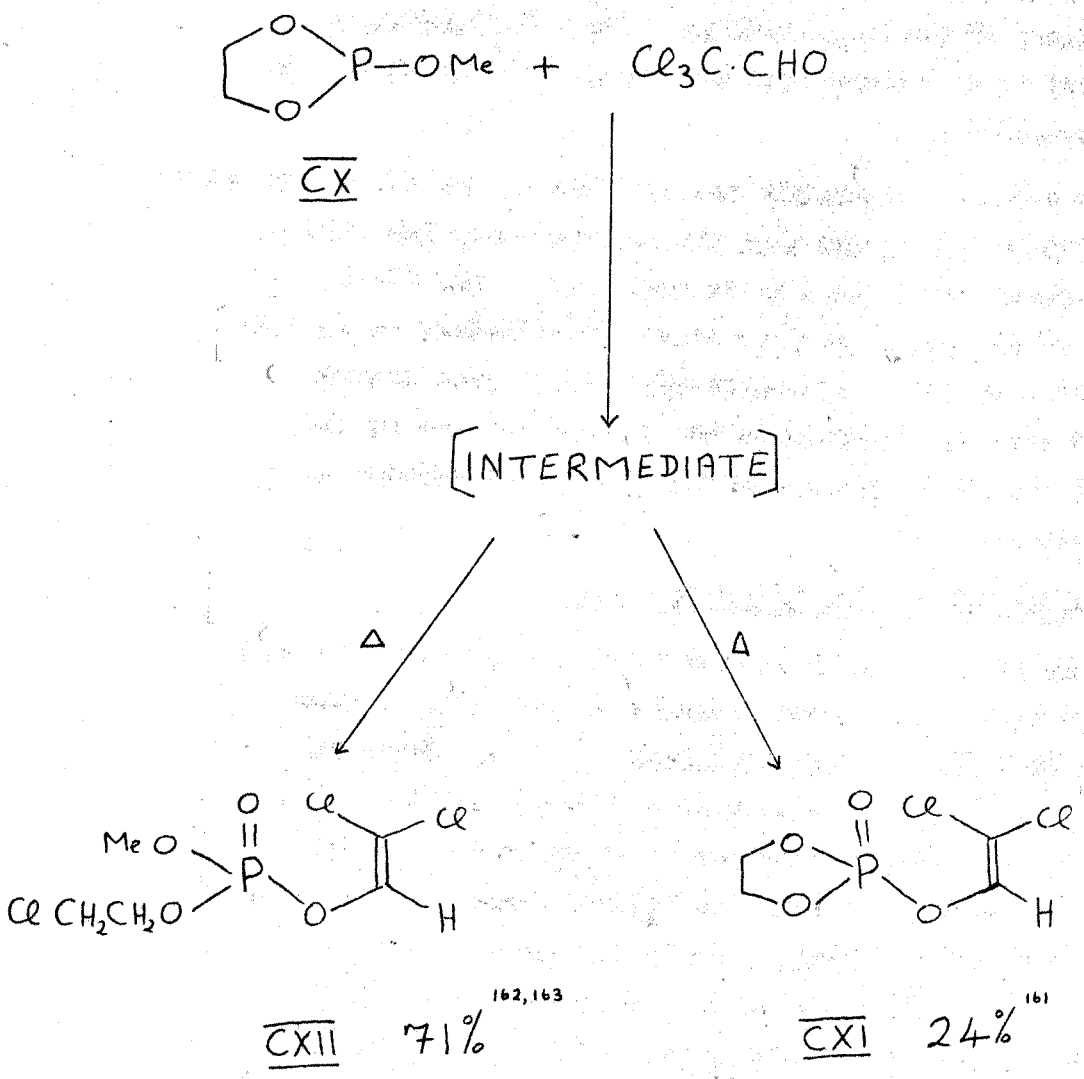
The isolation[120] of appreciable quantities of α-hydroxy-phosphonates from the reaction of chloroacetone with trimethyl phosphite in methanol or of bromoacetone with trimethyl phosphite in the presence of excess acetic acid is very compelling evidence

for the initial attack of the phosphite at the carbonyl carbon as the first step of the Perkow reaction. In contrast, phenacyl halides[73] did not appear to react in this manner; rather, in the presence of a fourfold excess of acetic acid, enol phosphate formation was greatly promoted at the expense of β-ketophosphonate.

In our work, the reactions between phenacyl halides and trialkyl phosphites in the presence of alcohols have been examined. We find that although α-hydroxy phosphonates are not formed as major products, there is strong evidence for their formation in trimethyl phosphite/methanol reactions. The results are summarised in Table IV.

TABLE IV

Phenacyl halide	Conditions	% Enol phosphate	% β-keto-phosphonate	% α-hydroxy-phosphonate
$PhCOCH_2Cl$	$(MeO)_3P$	95	5	-
"	$(MeO)_3P$; excess MeOH	63	10	27
"	$(EtO)_3P$	88	12	-
"	$(EtO)_3P$; excess EtOH	94	6	-
$PhCO\ CH_2\ Br$	$(MeO)_3P$	19	70	-
"	$(MeO)_3P$; excess MeOH	66	14	11
"	$(EtO)_3P$	21	74	-
"	$(EtO)_3P$; excess EtOH	71	18	-



CX

CXII 71%[162,163]

CXI 24%[161]

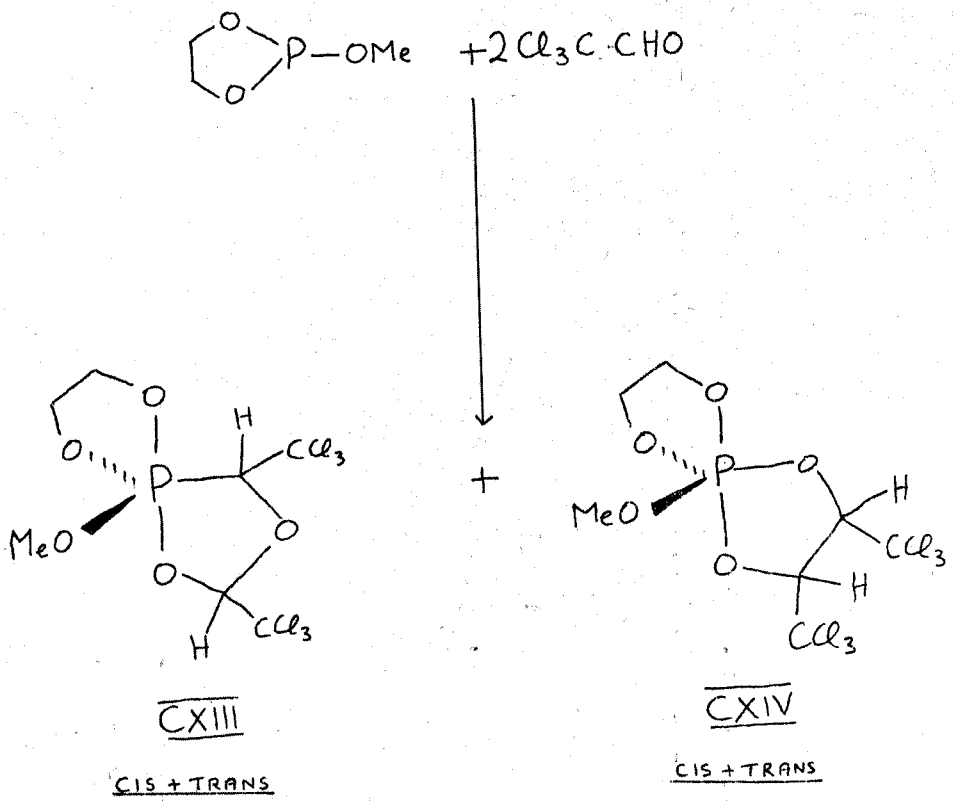
FIGURE XLIV

Protic solvents markedly improve the yields of enol phosphates at the expense of the corresponding β-ketophosphonate, a finding that is in keeping with earlier work[118] on other α-halocarbonyl compounds.

These results are readily accommodated by the scheme discussed earlier (Figure XX) except that the comparatively low yields of α-hydroxyphosphonates need to be explained. The steric influence of the phenyl residue could be sufficient to inhibit the formation of the α-hydroxyphosphonate to some extent. This point will be discussed in the context of some results concerning the structure and behaviour of intermediates in the Perkow reaction.

Intermediates in the Perkow Reaction

Though the studies summarised above may be useful in that they throw some light on the probable course of the Perkow reaction, they are far from definitive. In an effort to define more clearly the various steps which occur in the course of the reaction between α-halocarbonyl compounds and phosphites, we have attempted to characterise intermediates. In only one reported case had an intermediate in the Perkow reaction been noted[161]. Thus, reaction between ethylene methyl phosphite (CX) and chloral led to the formation of a waxy solid which, on heating, melted and finally decomposed to give what was cited as 24% of 2,2-dichlorovinyl ethylene phosphite (CXI); (Figure XLIV). Other workers[162,163] cite a yield of 71% of the ring-opened product, 2-chloroethyl 2,2-dichlorovinyl methyl phosphate (CXII). Lichtenthaler[102], in his comprehensive review of the field, has combined these reports and interpreted them as implying a 3:1 ratio of ring-opening to ring-retention in the dealkylation step.


P—OMe
+2 Cl3C·CHO
MeO
H
CCl3
CXIII
CIS + TRANS
CXIV
CIS + TRANS

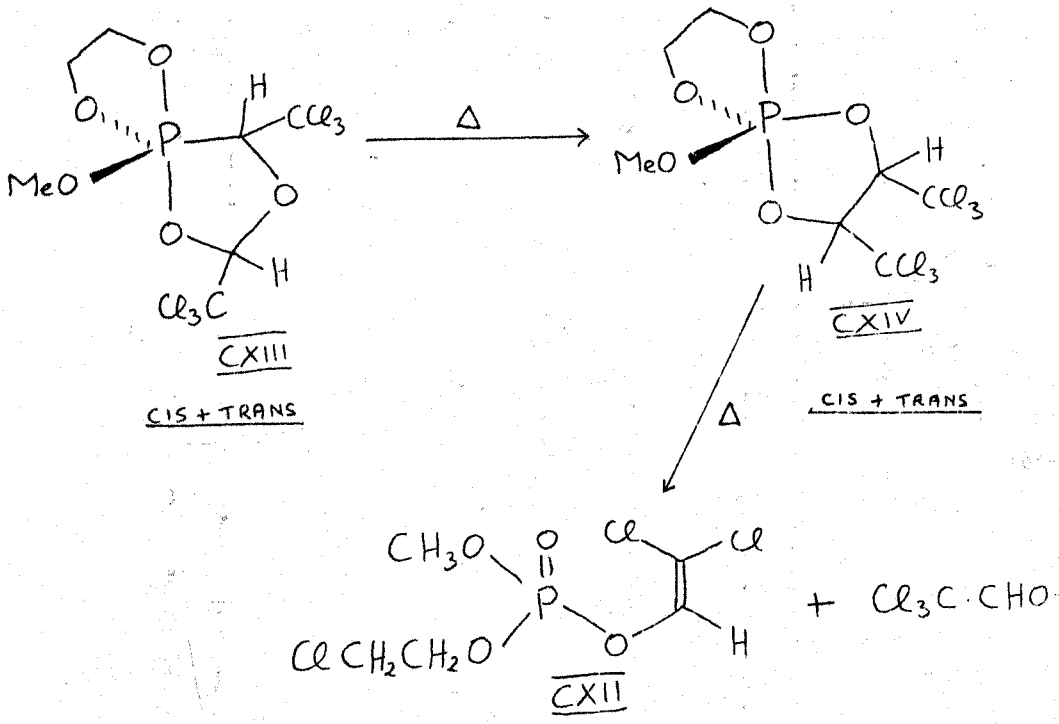

MeO
H
CCl3
Δ
Cl3C
CXIII
CIS + TRANS
CXIV
CIS + TRANS
CH3O
ClCH2CH2O
Cl
H
CXII
+ Cl3C·CHO

FIGURE XLV

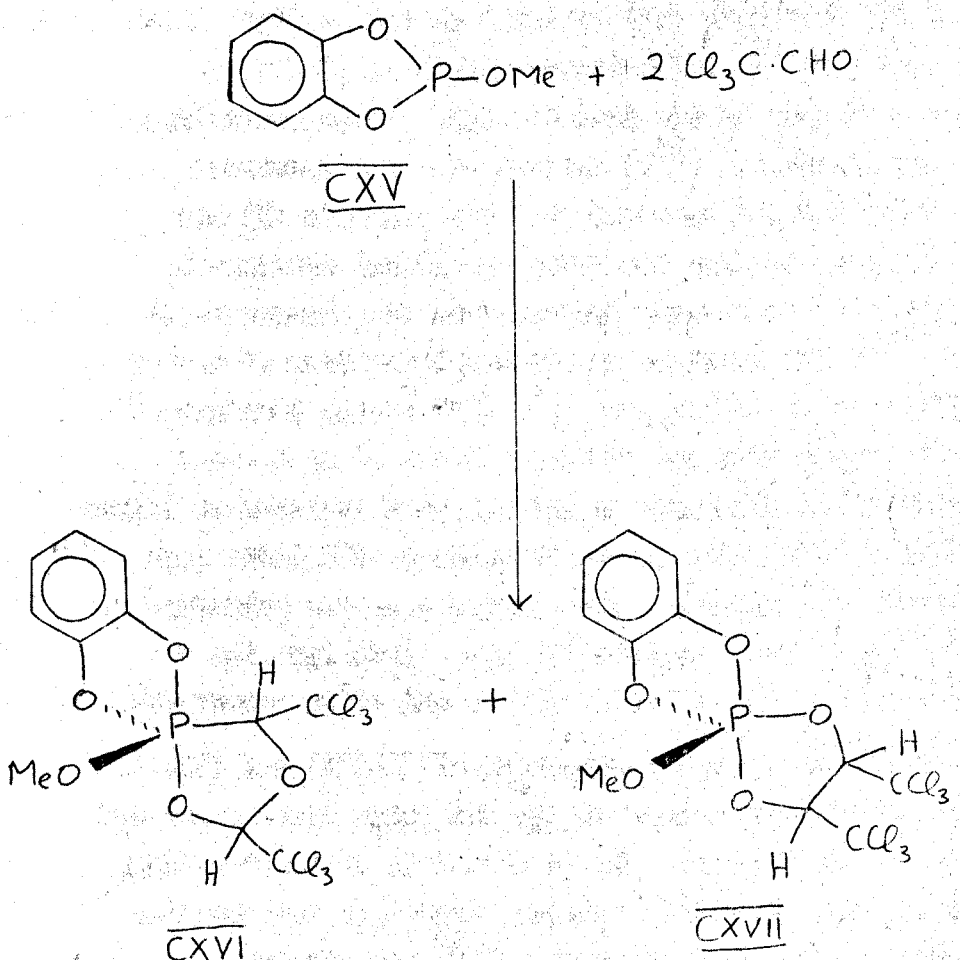


FIGURE XLVI

The reaction between (CX) and chloral has been reinvestigated and the course of the reaction and nature of the intermediate have become clear. Two equivalents of chloral reacted with one of the phosphite (CX) to yield an intermediate which is almost certainly the 1,4,2-dioxaphospholane (CXIII) in equilibrium with some of the isomeric 1,3,2-dioxaphospholane (CXIV). The phosphorus (^{31}P) nuclear magnetic resonance spectrum, infra-red and mass spectra (see Appendix II) and elemental analysis confirm the gross structural assignment. (Figure XLV). Of particular interest are the changes which occur in the ^{31}P NMR spectrum on warming a solution of one of the possible isomers (CXIII), to 33°C (NMR cavity temperature). Initially, a single peak was observed which, after a short time, diminished in intensity as another peak appeared at higher field, followed eventually by the appearance of a third peak at lower field than either. This latter peak was subsequently shown to be due to the phosphate (CXII). (See Appendix I for a discussion of the NMR data of this and other compounds).

Because of the rapid isomerisation of (CXIII) and (CXIV), an analysis of the proportions of cis and trans isomers was not possible by ^{1}H NMR studies. In an effort to circumvent this limitation we investigated the product formed by the reaction between methyl o-phenylene phosphite (CXI) and chloral. (Figure XLVI). This compound (CXVI), certainly a mixture of (CXVI) and (CXVII) in solution, was found to be somewhat more stable to moisture and oxygen. (CXVI) melted at 142°C at which temperature slow decomposition was discernible.

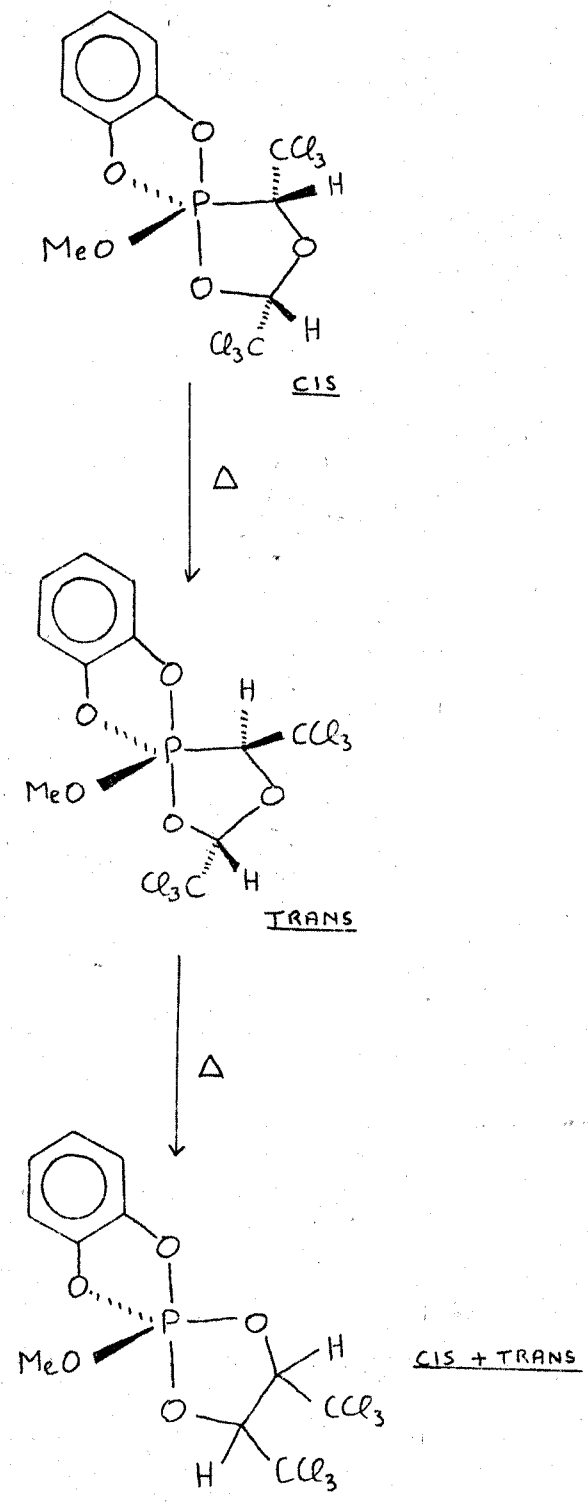


FIGURE XLVII

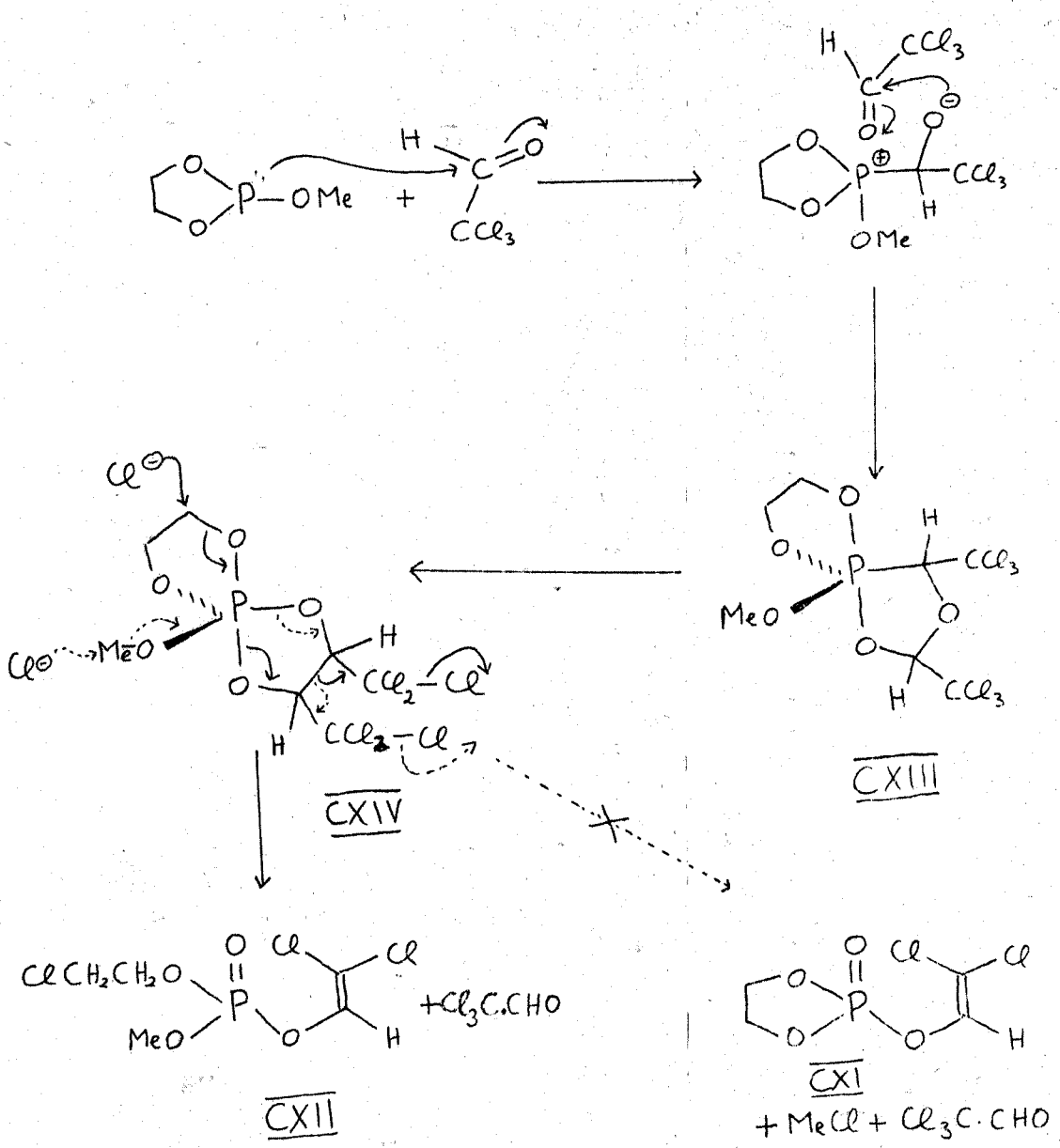
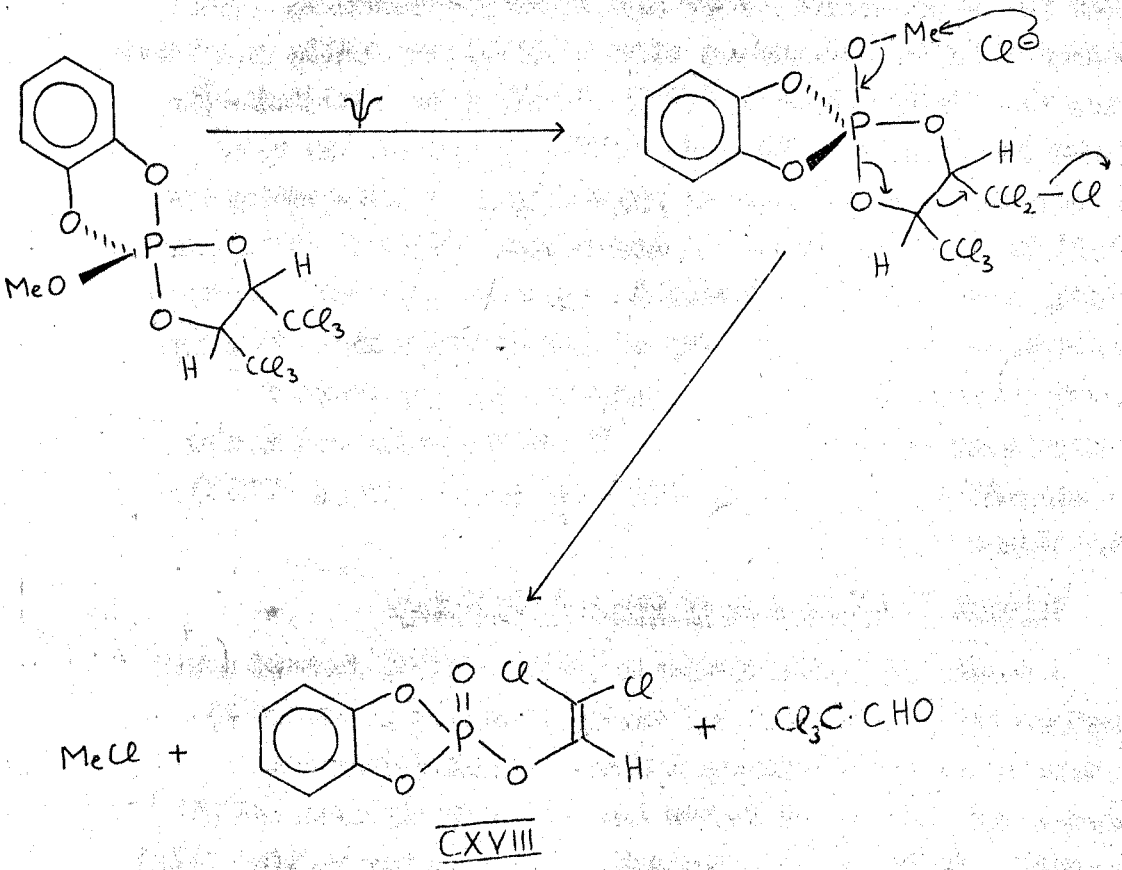


FIGURE XLVIII



CXVIII

FIGURE XLIX

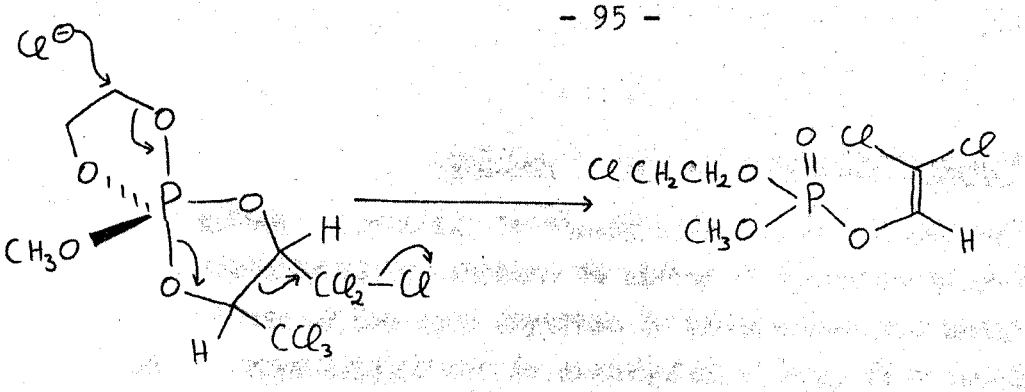
The greater stability of (CXVI) permitted a more careful NMR study of its behaviour in solution. The ^{31}P NMR studies showed that (CXVI) isomerised rapidly to (CXVII) (the assignments were made by analogy with related compounds[131,133,136] which itself underwent a very slow disproportionation, a peak corresponding to a phosphate ester (CXVIII) eventually appearing. Since the isomerisation of (CXVI) to (CXVII) was qualitatively slower than that of (CXIII) to (CXIV), an attempt was made to analyse the proportions of cis and trans isomers present in (CXVI) by ^{1}H NMR studies. A crystalline sample of (CXVI) was rapidly dissolved in preheated deuterochloroform and a spectrum immediately run. An analysis of this spectrum shows that cis (CXVI) probably crystallises preferentially (of Ramirez' observations on related systems[131]), subsequently undergoing isomerisation to both trans (CXVI) and cis and trans (CXVII). (See Figure XLVII).

Thermal decomposition of the intermediates

A sample of the intermediate (CXIII + CXIV) derived from ethylene methyl phosphite and chloral (melting point 100°C), on heating to 150°C decomposed almost quantitatively to chloral and (CXII), the latter identified by its mass and NMR spectra. (CXI) was not obtained. Further, the boiling point of (CXII) was found to be the same as that recorded by Allen and Johnson[161] for what they formulated as (CXI).

On the basis of the above results we felt confident that, in broad outline, the path of the reaction between (CX) and chloral could be formulated as shown in Figure (XLVIII).

Decomposition of (CXVI) under controlled conditions permitted the isolation of an almost quantitative amount of chloral but extensive decomposition of the residue precluded its characterisation. It is envisaged that decomposition occurs as in Figure (XLIX) but this has yet to be proved.

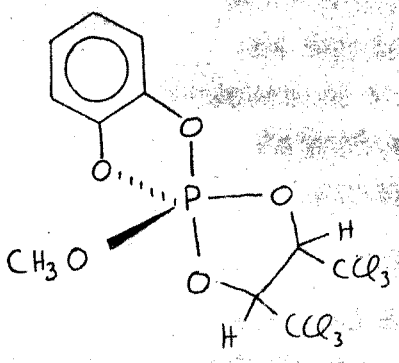


CXIV

(i) CIV IS DRAWN IN THE MOST FAVOURABLE CONFORMATION, ENERGETICALLY

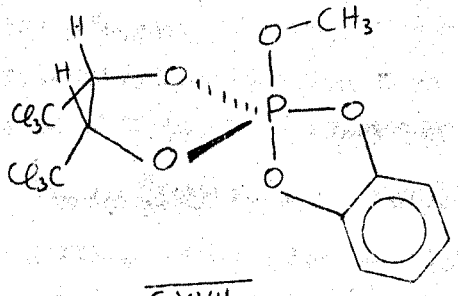
(ii) FRAGMENTATION PROCESSES OCCUR PREFERENTIALLY ALONG APICAL BONDS

(i)+(ii) EXPLAIN WHY ONLY THE RING-OPENED PRODUCT SHOULD BE OBSERVED



CXVII

DEALKYLATION IS AN ENERGETICALLY UNFAVOURABLE PROCESS IN THIS CONFORMATION SINCE THE -OMe GROUP IS EQUATORIAL.



CXVIIa

LOWEST ENERGY CONFORMATION, IN WHICH -OMe GROUP IN AN APICAL POSITION. STILL UNFAVOURABLE FOR DEALKYLATION BECAUSE THE "LEAVING" GROUP IS EQUATORIAL.

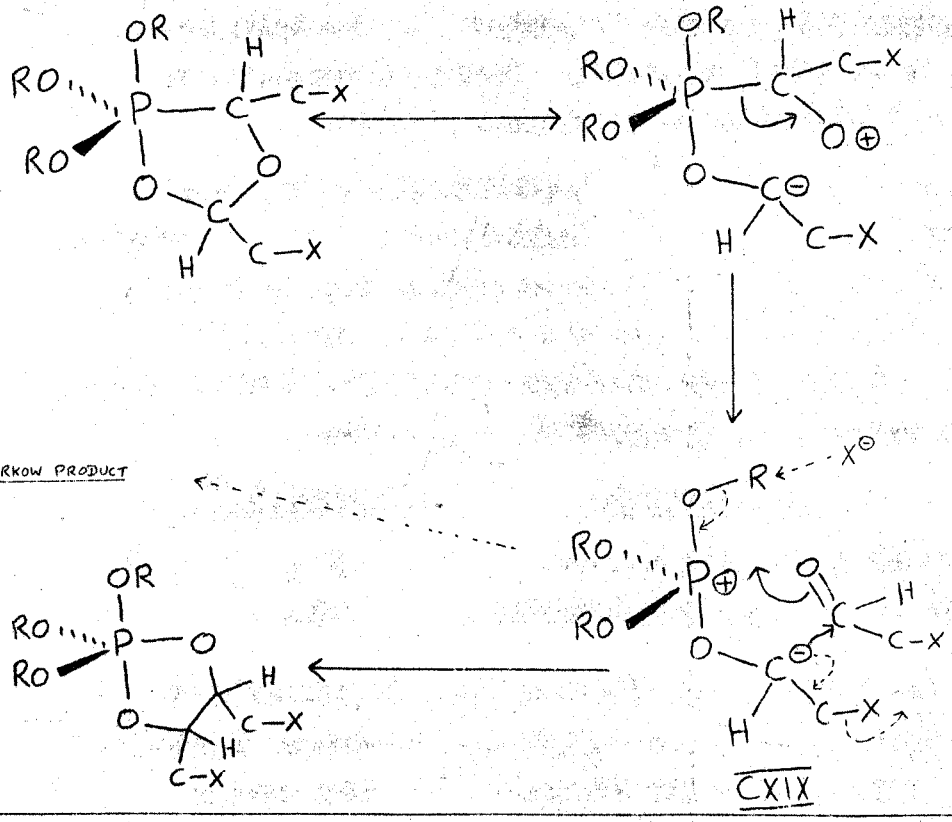
FIGURE I

Intermediates with acyclic phosphites

The results with cyclic phosphites were sufficiently encouraging to prompt a series of careful Perkow reactions (utilising two equivalents of carbonyl compound to one of phosphite) with acyclic phosphites at low temperatures. The residual solutions were subsequently examined by infra-red and ^{31}P NMR spectroscopy. In only one case (triethyl phosphite reacting with chloroacetone) was any evidence of a penta-covalent phosphorus intermediate obtained. The residue from this reaction exhibited, besides a single peak due to enol phosphate, a very small peak, which rapidly disappeared (~5% of major peak intensity) at approximately + 47 ppm relative to 85% H_3PO_4, a chemical shift characteristic of monocyclic phosphoranes[166]. This latter observation, though reproducible, is not unequivocal, since the signal to noise ratio was not high and the rapid disappearance of the peak precluded its enhancement by iterative scanning techniques. It is envisaged that use of a variable temperature accessory operating at low temperatures will be able to settle this question.

Mechanism of isomerisation and fragmentation

(CXVI) was synthesised since it was reasoned that the reduced flexional mobility of the unsaturated ring in (CXVI) and (CXVII) compared with the saturated ring in (CXIII) and (CXIV) should provide a barrier to the pseudorotation[157,167] of the molecule, this process being the one most reasonably invoked to explain the fragmentation pathways of these molecules (Figure I).


PERKOW PRODUCT
CXIX

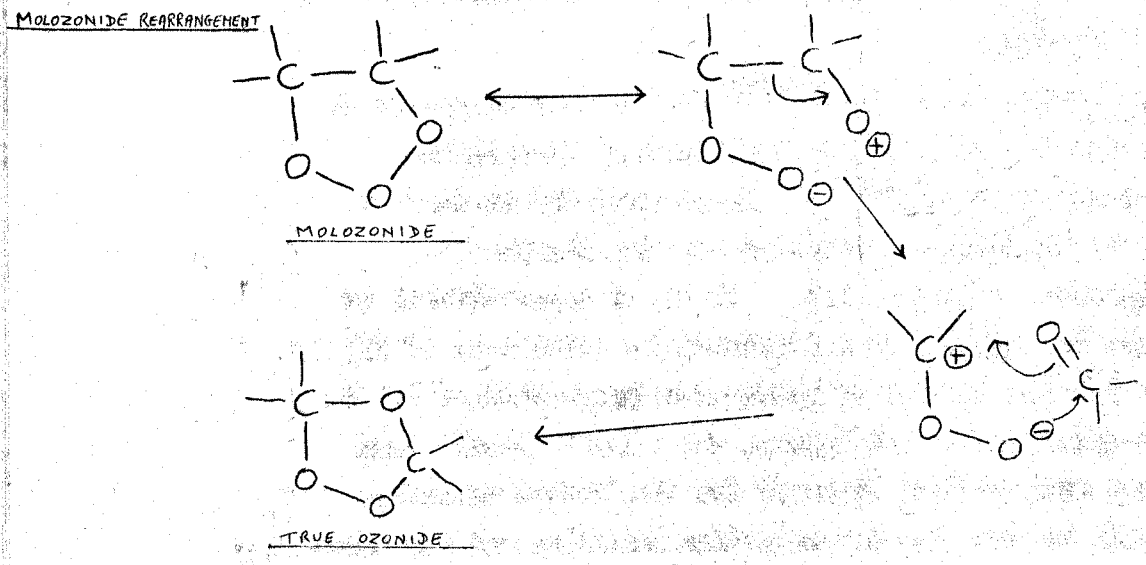

MOLOZONIDE REARRANGEMENT
MOLOZONIDE
TRUE OZONIDE

FIGURE LI

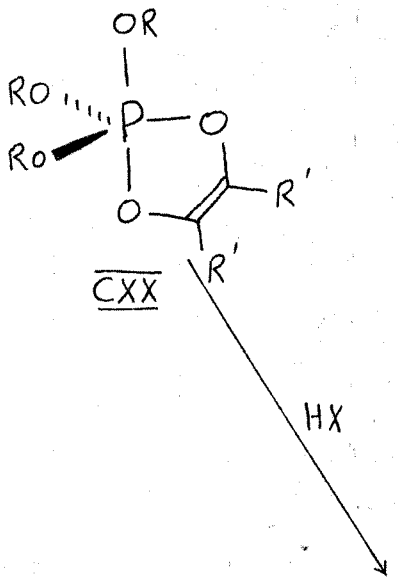
From Figure (L) it can be seen that (CXVII) cannot take up an energetically favourable conformation for dealkylation to occur in an apical direction. Hence the dealkylation process is inhibited by an extra energy barrier.

The mechanism by which a 1,4,2-dioxaphospholane can be transformed into a 1,3,2-dioxaphospholane is much less apparent. As pointed out earlier, there is an analogy between such a process and the isomerisation of a molozonide to a "true ozonide". A bond energy calculation shows that both of these processes appear to be energetically favourable.

Transformation	ΔG (kcal.mole^{-1})
molozonide ⟶ true ozonide	53.4
1,4,2- ⟶ 1,3,2-dioxaphospholane	19.1

All the evidence from this and other[136] work seems to indicate that the 1,4,2- ⟶ 1,3,2-dioxaphospholane isomerisation is as specific as the molozonide ⟶ true ozonide isomerisation, both, in the absence of other reagents, giving only one product.

The Criegee mechanism[141,168] for the rearrangement of molozonides to true ozonides has received appreciable experimental support[168,170]. It is possible to draw an analogy to the Criegee mechanism for the phosphorane rearrangement (Figure LI). It is of some interest to note that the hypothetical intermediate zwitterion (CXIX) is capable (dotted arrows) of undergoing fragmentation to an enol phosphate and alkyl halide, the overall result thus being the same as that observed for the Perkow reaction. It could well be that the isomerisation reaction and the irreversible fragmentation reaction share a common first step.

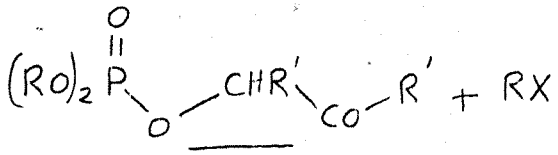


CXX

$R'.CHX.CO.R'$ + $(RO)_3P=O$

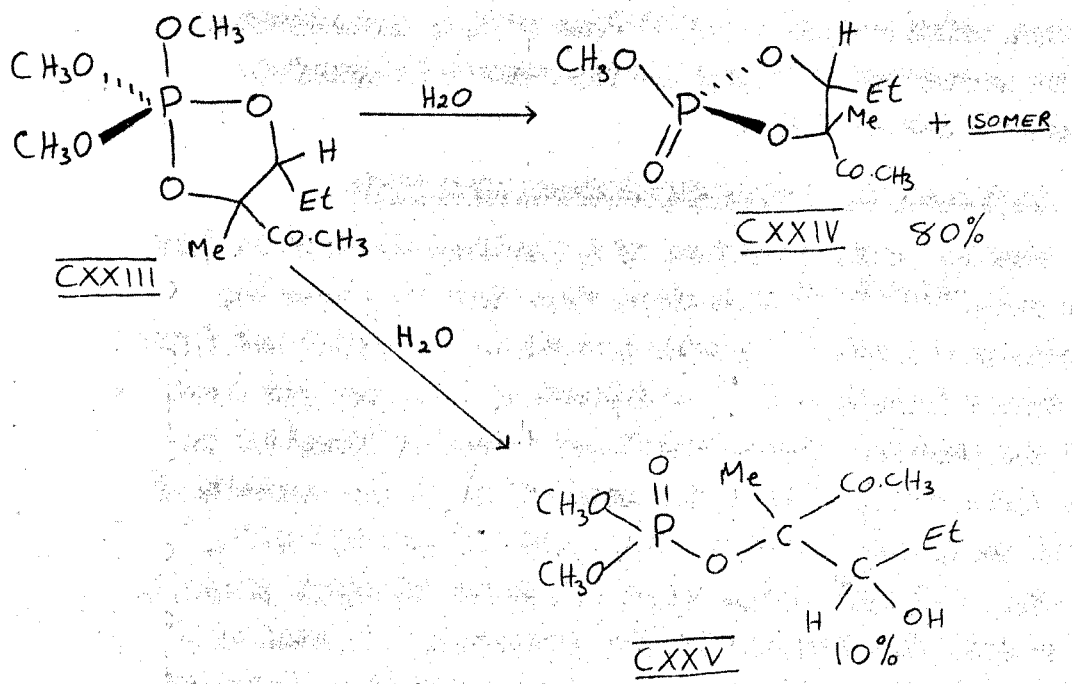
CXXI

AND



CXXII

FIGURE LII



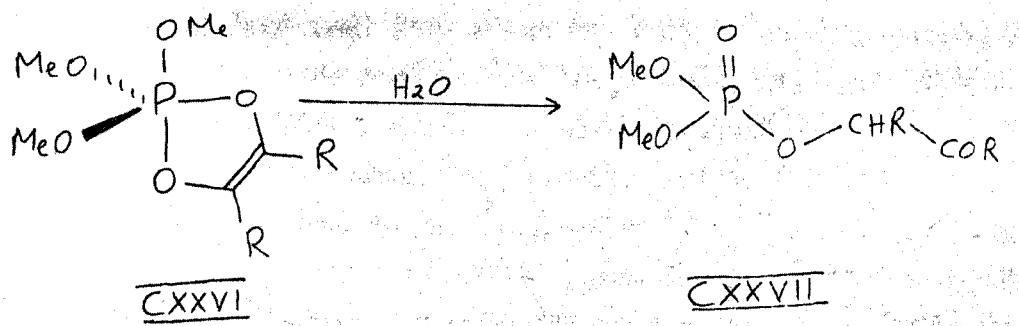


FIGURE LIII

However, until more detailed studies of this isomerisation can be undertaken it is perhaps inadvisable to speculate concerning its mechanism.

Reactions of pentaoxyphosphoranes with acids

Studies of the reactions of 1,3,2-dioxaphospholenes (CXX) with acids[125,171-173] have shown that, depending upon the substituents R and R^1, varying proportions of (CXXI) and (CXXII) are formed (Figure LII). In support of this, we have found that the reaction between benzil and trimethyl phosphite to form (CXX; R=CH_3, R^1=Ph), when carried out in the presence of acetic acid, gave directly a high yield of (CXXII); R=CH_3, R^1 = Ph). Surprisingly, reaction between trimethyl phosphite and benzil, in methylene chloride previously saturated with anhydrous hydrogen chloride, seemed to occur reluctantly, if at all, a good recovery of starting material being achieved.

Ramirez[174,175] has studied the hydrolysis of saturated pentaoxyphosphoranes (e.g. CXXIII) and shown that they tend to yield the cyclic phosphate ester (CXIV) rather than the corresponding open chain compound (CXXV). (Figure LIII). This is in sharp contrast to the behaviour of unsaturated phosphoranes (e.g. CXXVI; R=CH_3) which gave the open-chain ester (CXXVII; R=CH_3)[175]. Similarly, interaction of (CXXVI; R=H) with anhydrous hydrogen chloride in benzene[175] yielded 75% of (CXXVII; R=H). No (CXXI; R^1=H,X=Cl) was observed in this reaction.

In view of the above investigations it was felt that if a "normal" Perkow reaction proceeded by way of a pentacovalent phosphorus intermediate, then carrying out the reaction in the presence of excess hydrogen chloride might lead to the appearance

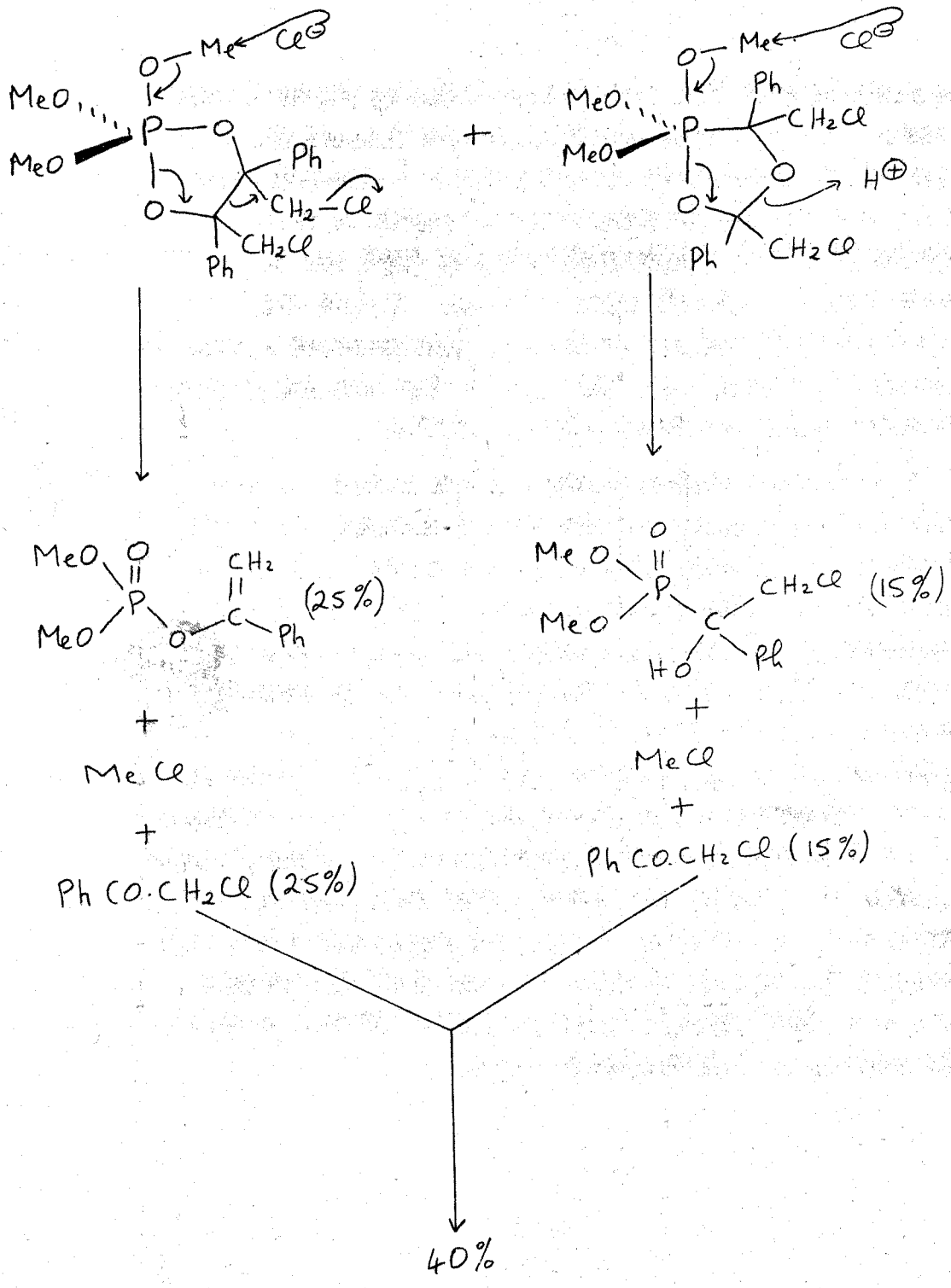

MeO
MeO
Me
Cl⊖
Ph
CH2Cl
CH2
Cl
H⊕
(25%)
(15%)
MeCl
PhCO.CH2Cl (25%)
PhCO.CH2Cl (15%)
40%

FIGURE LIV

of products derived from such intermediates by reaction with the acid. In the event, reaction between phenacyl chloride and trimethyl phosphite in methylene chloride saturated with hydrogen chloride led to relatively low yields of enol phosphate (25%) and α-hydroxyphosphonate (15%) and the recovery of 50% of the phenacyl chloride. Whilst this result can be rationalised in terms of pentacovalent phosphorus intermediates (Figure LIV), the evidence for such intermediates in "normal" Perkow reactions remains doubtful.

If the "normal" Perkow reaction should follow a course similar to that outlined for the chloral reactions discussed earlier, then a somewhat more reasonable explanation can be advanced for the lower yields of α-hydroxyphosphonates in the reaction between phenacyl halides and phosphites in the presence of methanol than in the corresponding haloacetone reactions. The most feasible pathway to α-hydroxy-phosphonates (as shown in Figure LIV) is <u>via</u> a 1,4,2-dioxaphospholane. It is reasonable that bulky groups α to the halogen-bearing carbon will increase steric compression in the phospholane, thus facilitating the isomerisation to a 1,3,2-dioxaphospholane. Accordingly, the proportions of the latter will increase at the expense of the former and dealkylation will produce a correspondingly greater proportion of enol phosphate at the expense of α-hydroxyphosphonate.

EXPERIMENTAL

EXPERIMENTAL

INTRODUCTION

Abbreviations

The following abbreviations are used in the text of the experimental section:-

M.Pt.	melting point
B.Pt.	boiling point
M.Wt.	molecular weight
gm., mgm.	gram, milligram
mmole	millimole
M, N	molar, normal

I.R. Spectra

ν (cm^{-1})	frequency of absorption maxima, in wave numbers
s, m, w	strong, medium, weak absorptions

U.V. Spectra

λ max (nm)	wavelength of absorption, in nanometres

NMR Spectra

ppm	parts per million
δ	delta values (in ppm) relative to 85% H_3PO_4=0.0 ppm (Chemical shifts of ^{31}P nuclei)
TFA	trifluoracetic acid
TMS	tetra methyl silane
τ	tau values of peaks based on TMS = 10.0
J (c/s)	Spin-spin coupling constant in cycles per second

Mass Spectra

M^+	molecular ion
m/e	mass-to-charge ratio, in atomic units
m^* (X⟶ Y)	metastable peak (transition causing the peak)

CHROMATOGRAPHY

Gas liquid chromatography (GLC) was carried out on an F + M model instrument with a thermal conductivity detector

Paper chromatography was carried out by the descending technique in one of three systems:

System A: n-BuOH: AcOH: H_2O (5:2:3)

System B: Pyridine: H_2O (13:11)

System C: iso-PrOH: NH_4OH: H_2O (7:1:2)

SPECTRA

I.R. Spectra were recorded on Perkin Elmer 337, 257 or 457 instruments.

U.V. Spectra were recorded using a Unicam SP800 spectrophotometer.

NMR Spectra were recorded using a Perkin Elmer R10 spectrometer operating at 60 Mc/s (^1H) or 24.2907 Mc/s (^{31}P).

Mass spectra were recorded at the University of Hull on an A.E.I. M.S.9 instrument.

Melting points a re uncorrected.

SYNTHESIS OF AMINOPHOSPHONIC ACIDS AND DERIVATIVES

A. Kosolapoff procedure

N-(2-bromoethyl) phthalimide (5.08 gm., 20 mmole) was treated with triethyl phosphite (3.75 ml; 3.65 gm., 22 mmole) and the mixture heated to 160°C for 5 hours. The evolved ethyl bromide was distilled from the reaction mixture and collected in an ice-salt cooled trap. (Weight collected = 2.10 gm; 96%). The residual brown oil was treated with conc. HCl (30 ml) and H_2O (10 ml), the solution boiled under reflux for 48 hours, cooled, filtered, treated with charcoal, boiled, refiltered and evaporated to give a dark brown oil. Examination by paper chromatography (System A) showed a streak of phosphorus containing material from the origin to the solvent front with main absorptions at R_F 0.35, 0.51 and 0.78. The oil was dissolved in water (10 ml) and applied to a column of Dowex 50 (H^+) (5 x 50 cm). Elution with water removed most of the coloured material. When the eluate was neutral 200 ml of eluate contained all the AEP (R_F 0.25 in System A). The solution was acidified with 0.1N HCl, concentrated (rotovac.) and freeze-dried to give a white powder (0.63 gm, 25%) having M.Pt. 197-208°dec. After recrystallisation from aqueous acetone, 0.5 gm (20%) of colourless crystals having M.Pt. 289-93° dec. were obtained.

B. Chavane procedure

Diethyl phosphite (13.8 gm., 0.1 mole) was dissolved in benzene (25 ml). Sodium wire (3 gm., excess) was added and the solution boiled under reflux for 5 hours. The solution was decanted from the undissolved sodium and treated with N-(2-bromoethyl)phthalimide (25.4 gm., 0.1 mole). The solution, which rapidly clouded, was boiled under reflux for 10 hours, cooled, the precipitated NaBr filtered off and the solution evaporated to give a pale yellow oil. This oil was dissolved in conc. HCl (100 ml) and the solution boiled under reflux for 48 hours. After cooling, the precipitated phthalic acid (15.8 gm; 95%) was filtered off, the solution treated with charcoal, boiled, filtered and evaporated to give a pale yellow oil, (4.3 gm). The oil was dissolved in EtOH (20 ml) and the solution treated with 1,2-epoxy propane causing precipitation of a tacky solid which was dissolved in water (3.5 ml) and the solution treated with acetone, dropwise. An oil separated but on cooling to 0°C overnight the oil crystallised to give 1.7 gm. of a colourless solid having M.Pt. 200-10° dec. Recrystallisation from aqueous acetone gave 1.3 gm. (10.4%) having M.Pt. 291-6°dec.

C. N-phthalyl AEP

AEP (250 mgm., 2.0 mmole) and phthalic anhydride (296 mgm., 2.0 mmole) were heated together at 150-180°C under a vacuum (25 mm. Hg.) for 30 minutes. Initially (~3 minutes) a solution formed which evolved a gas and became opaque, finally resolidifying. The residual solid was crushed and re-crystallised from isopropanol/hexane (1:1) to give 0.499 gm. (97%) of colourless crystals having M.Pt. 198-9°C (lit.[213] M.Pt. 198.5-199.5°C), R_F (System A) 0.75.

Hydrolysis of N-phthalyl AEP in conc. HCl gave only one phosphorus containing spot chromatographically, R_F (System A) 0.25, and a quantitative yield of phthalic acid.

D. New synthetic procedure

Materials

All the nitriles employed were obtained commercially and used without further purification.

Triethyl phosphite was obtained commercially and distilled from molecular sieves, a 1°C fraction boiling in the range 155-160°C (depending on the prevailing atmospheric pressure) being collected and used.

Diethyl cyanomethyl phosphonate

A mixture of triethyl phosphite (1.32 mole) and chloroacetonitrile (1.32 mole) was heated at 150°C for 14 hours. Vacuum distillation gave diethyl cyanomethyl phosphonate, B.Pt. 98-100°C/0.1 mm., 218 gm., (93.5%) (lit[197] B.Pt. 126-7°C/2 mm).

ν (liquid film) 2970 (m) 2920 (m) 2865 (m)
2260 (m) 1460 (m) 1275 (s) 1185 (m)
1040 (s, broad) 865 (m) 567 (m-s) cm^{-1}

τ (neat) 5.88 (multiplet) 4H
7.0-8.15 (multiplet) 4H
8.70 (triplet, J=7.3 c/s) 6H

δ (neat) -15.5 ppm

Diethyl 2-aminoethyl phosphonate

To a solution of diethyl cyanomethyl phosphonate (88.5 gm; 0.5 mole) in ethanol (A.R., 300 ml) saturated with gaseous ammonia was added settled Raney nickel suspension (20 ml) in ethanol and the mixture shaken in H_2 (110 atmospheres, 40-65°C) in a 1 litre autoclave for 15 hours. After filtration and evaporation, the residue was distilled <u>in vacuo</u> to give diethyl 2-aminoethyl phosphonate, B.Pt. 75-80°C/0.6 mm., 59.4 gm. (66%) (lit[178] B.Pt. 93-5°C/4 mm).

ν (thin film)	3360 (m, broad) 3295 (m, broad)
	2980 (s) 1605 (s) 1230 (s, broad)
	1050, 1025 (s, broad) 953 (s) cm^{-1}
τ (neat)	5.95 (multiplet) 4H
	7.21 (multiplet) 2H
	8.10 (multiplet) 2H
	8.35 (singlet) 2H
	8.75 (triplet, J=7.5c/s) 3H
δ (neat)	-18.6 ppm

2-aminoethyl phosphonic acid

Diethyl 2-aminoethylphosphonate (32 gm; 0.177 mole) was heated vigorously under reflux with excess 48% HBr, the condenser being occasionally removed to permit the escape of ethanol (otherwise, the solution stops refluxing due to the cooling imparted by evaporation of the ethanol). After 13 hours the solvent was evaporated to yield a crystalline solid which was redissolved in water, the solution decolourised with charcoal and filtered into excess cold acetone. An oil separated, which, on addition of a few drops of 1,2-epoxypropane, crystallised slowly.

First crop. 21.0 gm (95%) M.Pt. 285-6°C

Evaporation of the mother liquors yielded an oil which was dissolved in the minimum of boiling water. Cold methanol was added slowly to this solution until cloudiness developed. On standing, a further 1.04 gm. (4.5%) of crystals separated, M.Pt. 285-6°C (lit.[1,3,7,10,11,15,16,53,54] M.Pts. range from 250-299°C).

Total yield = 99.5%

Analysis

$C_2H_8NO_3P$	requires	C, 19.2; H, 6.4; N, 11.2; P, 24.8%
	found	C, 19.21; H, 6.57; N, 11.16; P, 24.88%
ν (KBr pellet)		Identical to published spectrum[187]
τ (D_2O)		6.95, 7.10 (doublet of triplets; J_{HH} = 8.0 c/s J_{PH} = 10.5 c/s) 2H
		7.88-8.58 (multiplet) 2H
Chromatography		R_F 0.25 (System A)
		R_F 0.55 (System B)

Diethyl 2-dimethylaminoethylphosphonate methiodide was prepared in a manner analogous to the described method[179]. Diethyl 2-aminoethyl phosphonate (18.2 gm) was converted into the N,N-dimethyl compound which, without isolation, was treated with iodomethane to yield the methiodide, 23.36 gm. (67.8%), having M.Pt. 163-4°C. Recrystallisation from ethyl acetate/methanol gave colourless leaves, M.Pt. 164-5°C, (lit.[180] M.Pt. 156-7°C).

Analysis

$C_9H_{23}NO_3PI$	requires	C,30.80; H, 6.56; N, 3.99; I,36.20;P,8.83%
	found	C,31.04; H, 6.39; N, 4.17; I,36.14;P,8.89%

Dealkylation of diethyl 2-dimethylaminoethyl phosphonate methiodide

The methiodide (3.51 gm; 10 mmole) was heated, in a flask, to 180°C under a vacuum pressure of 0.005 mm for 2 hours. The evolved gas was passed through a liquid N_2 cooled trap. After cooling, the frothy residue weighed 2.01 gm. (Theoretical weight 1.95 gm). The trap contained 1.50 gm. ethyl iodide (confirmed by comparison of IR and NMR spectra with standard spectra). The froth was dissolved in methanol (10 ml) and the solution treated with ethyl acetate to give a sticky solid (1.31 gm) having M.Pt. 280°C. This solid could not be satisfactorily crystallised.

2-trimethylammonium ethyl phosphonic acid betaine

Diethyl 2-dimethylaminoethyl phosphonate methiodide (17.55 gm: 0.05 mole) was dissolved in excess 48% HBr. The solution was heated under reflux for 24 hours, the solvent evaporated and the residual oil dissolved in EtOH (30 ml). Removal of the last traces of mineral acid by the addition of a few drops of 1,2-epoxypropane gave a mass of colourless crystals. Recrystallisation from aqueous ethanol yielded 2-trimethylammonium ethyl phosphonic acid betaine, 6.93 gm (83%) M.Pt. 251-2°dec. (lit.[180] M.Pt. 250-2°dec.) which crystallised as the dihydrate[6].

Analysis

$C_5H_{14}NO_3P.2H_2O$	requires	C, 29.55; H, 8.86; N,6.90; P, 15.28%
	found	C, 29.21; H, 8.50; N, 6.80; P,15.10%
ν (KBr pellet)		Identical to published spectrum[180]

Homologous compounds were synthesised by the procedures described above. Relevant data are gathered in Table V.

TABLE V

Compound	Yield	M.Pt./B.Pt.	Lit.M.Pt./B.Pt.
$(EtO)_2P(=O)(CH_2)_2CN$	59%	100°C/0.2mm	128°/2mm,[192] 160°/10mm[181]
$(EtO)_2P(=O)(CH_2)_3NH_2$ *	96%	111°/0.9mm	-
$(EtO)_2P(=O)(CH_2)_3CN$	50%	128-132°/0.6mm	Not given
$(HO)_2P(=O)(CH_2)_3NH_2$	96%	289-90°dec.	274°dec.[191]
$(EtO)_2P(=O)(CH_2)_3\overset{+}{N}Me_3\ \overset{-}{I}$	40%	108-10° (170°dec.)	109-11°C
$(EtO)_2P(=O)(CH_2)_4NH_2$	20%	135°/0.8mm	-
$HO(-O)P(=O)(CH_2)_3\overset{+}{N}Me_3$	80%	276-7°C	277-8°C[180]

* Diethyl 3-aminopropyl phosphonate, on standing at room temperature for several weeks, deposited a crystalline solid having M.Pt. 245-6°C.

Analysis

$C_5H_{12}NO_2P$ requires	C, 40.3; H, 8.05; N, 9.40; P, 20.80%	
found	C, 40.0; H, 8.10; N, 9.56; P, 21.03%	
τ (D_2O)	5.87 (sextet, J = 7 c/s)	2H
	7.15 (triplet, J = 6.5 c/s)	6H
	8.45 (multiplet)	
	8.65 (triplet, J = 6.9 c/s)	3H
τ (TFA)	3.05 (broad singlet)	2H
	5.87 (quintet?)	2H
	7.07 (sextet?)	6H
	8.25 (multiplet)	
	8.80 (triplet, J = 6.9 c/s)	3H
δ (D_2O)	- 24.8 ppm	
Chromatography	R_F 0.58 (System A)	
	R_F 0.68 (System B)	
	R_F 0.62 (System C)	

2-amino-3-phosphono propionic acid was prepared by the method of Chambers and Isbell[184] via 2,2-diacetamidopropionic acid and thence α-acetamido acrylic acid to yield material, which, after recrystallisation from aqueous isopropanol had M.Pt. 233-4°dec. (lit.[184] M.Pt. 228°dec).

Analysis

$C_3H_8NO_5P$ requires	C, 21.15; H, 5.07; N, 8.20; P, 18.38%	
found	C, 21.3; H, 4.74; N, 8.29; P, 18.3%	

DIAZOTISATION OF AEP

AEP (250 mgm) was diazotised using excess $NaNO_2$/HCl, the solution being maintained at 0-5°C during the reaction. After 5 hours, paper chromatographic examination (System A) of the reaction mixture showed that there were two phosphorus-containing components. Both of these spots gave an immediate yellow colouration with Ha nes-Isherwood[185,186] spray, subsequently turning blue.

R_F 0.25 (trace; AEP)

R_F 0.53 (main component)

(2-chloroethyl phosphonic acid had R_F 0.63 in this system)

The solution was concentrated by freeze-drying, applied to an AG11A8 ion-retardation resin column (1x50 cm) and eluted with water. 5 ml fractions were collected and examined chromatographically in an ascending system A, using a glass spiral to hold the paper in a closed beaker[187]. Fractions 1-12 contained only inorganic orthophosphate (R_F 0.33), no other phosphorus containing fractions being obtained. Evidently, decomposition of the compound of R_F 0.53 had occurred on the column.

Repetition of the above experiment using different conditions eventually demonstrated that the material of R_F 0.53 (System A) could be eluted with dilute HCl. (0.05 N). Above pH4

decomposition became quite rapid. Below pH2 the compound seemed indefinitely stable.

Attempted isolation of AEP diazotisation product

1a A dilute HCl solution of the diazotisation product was evaporated to dryness at 35°C. The residual oil began to evolve a gas some 50 seconds after the vacuum had been released. Chromatographic examination of the residue showed it to be orthophosphoric acid. (R_F 0.33 in System A).

1b The above experiment was repeated but with the addition that N_2 was swept through the flask after evaporation, the effluent gases being passed into a solution of bromine in carbon tetrachloride. The CCl_4 solution was subsequently subjected to examination by GLC, against a standard sample of 1,2-dibromoethane in CCl_4. The Br_2/CCl_4 solution exhibited a peak which had an identical retention time to that of 1,2-dibromoethane.

2a A dilute HCl solution of the diazotisation product was freeze-dried, yielding a pale yellow oil which contained orthophosphoric acid as its only phosphorus containing component (System A).

2b The above experiment was repeated but the freeze-drying process was stopped before all the H_2O had been removed. Addition of ethanol produced a precipitate which rapidly changed to an oil and decomposed. The final product was orthophosphoric acid.

2c Treatment of a concentrated solution of the AEP diazotisation product in dilute HCl (obtained by partial freeze-drying) with ethanolic solutions of various organic and inorganic bases was attempted. The results are tabulated below.

Base	Effect	Chromatography (System A) of residue
Pyridine	Precipitate (White)	Pi
Cyclohexylamine	Precipitate (White)	Pi + R_F 0.53 material (1:1)
N-methylaniline	None visible	Solution contained only Pi
KOH (Aqueous EtOH)	Gas evolved Precipitate (White)	Pi Pi + R_F 0.53 material (4:1)
$Ba(OH)_2$ (Aqueous ethanol)	Precipitate (trace)	Pi; solution contained material R_F 0.53 + Pi
$BaCl_2$		

3. The cyclohexylammonium salt (containing both Pi and material of R_F 0.53) was dissolved in water. Chromatographic examination of this solution showed that the spot at R_F 0.53 had disappeared.

ATTEMPTED SYNTHESES OF 2-HYDROXYETHYL PHOSPHONIC ACID

1. Diethyl 2-acetoxy ethyl phosphonate was prepared from 2-bromoethyl acetate and triethyl phosphite[188] in 70% yield, having B.Pt. 150-152°C/15 mm. (lit.[188] B.Pt. 162°C/20 mm).

I.R. - Identical to published data.

(a) Diethyl 2-acetoxy ethyl phosphonate (1.0 gm) was boiled under reflux in concentrated HCl (20 ml) for 12 hours. Evaporation of the solvent yielded a colourless oil, chromatographic examination of which (System A) showed a number of phosphorus-containing components, one of which had R_F 0.53 and exhibited the same behaviour on spraying with the Hanes-Isherwood phosphate spray. This component was a minor constituent of the mixture.

(b) Diethyl 2-acetoxyethyl phosphonate (1.0 gm) was dissolved in concentrated HCl (20 ml) and the solution was stirred at room temperature. Daily chromatographic examination of this solution showed that hydrolysis of the acetoxy group occurred almost exclusively. Treatment of aliquots with NaOH solution (4N) to pH 12

resulted in gas evolution and the appearance of a new single chromatographic component. The results are tabulated below.

System	R_F(HCl solution)	R_F(starting material)	R_F(after NaOH)
A	0.86	0.95	0.61
B	0.77	0.94	0.61
C	0.65	0.83	0.72

Evaporation of the bulk of the hydrolysis solution gave diethyl 2-hydroxyethyl phosphonate (not purified further).

ν (liquid film) 3360 (s, broad) 1455 (m) 1280 (s) 1150 (s) 1040 (s, broad) 980 (s) 860 (m) 530 (m) cm^{-1}

τ (neat) 5.55 – 6.55 (multiplet) 6H

*7.55 – 8.35 (multiplet) 2H

8.65 (triplet, J = 6.9 c/s) 6H

* Higher resolution, resolved into a doublet of triplets, J_{PH} = 18.6 c/s

J_{HH} = 7.5 c/s

τ (D_2O) 5.50 – 6.60 (multiplet) 6H

7.50 – 8.30 (multiplet) 2H

8.70 (triplet, J = 6.9 c/s) 6H

τ (TFA) 3.85 (singlet) 2H

5.45 - 6.45 (multiplet) 6H

7.45 - 8.35 (multiplet) 2H

8.68 (triplet, J = 6.9 c/s) 6H

2. From 2-bromoethyl phosphonic acid

Diethyl 2-bromoethyl phosphonate was prepared from 1,2-dibromoethane and triethyl phosphite[189] in 56% yield, having B.Pt. 94-6°/0.5 mm (lit.[189] B.Pt. 101°/0.8 mm).

δ (neat) -25.5 ppm (lit.[209] = -28.5 ppm)

Hydrolysis of diethyl 2-bromoethyl phosphonate with concentrated HCl gave an almost quantitative yield of crude 2-bromoethyl phosphonic acid. Recrystallisation from chloroform gave material having M.Pt. 93-4°C (lit.[190] M.Pt. 86-7°C).

Treatment of 2-bromoethyl phosphonic acid with silver salts

A. (i) Silver nitrate

2-bromoethyl phosphonic acid (1.0 gm; 5.3 mmole) was dissolved in water (10 ml), to which solution was added $AgNO_3$ (0.9 gm; 5.3 mmole). The solution was stirred for 3 days at ambient temperature after which time chromatographic examination showed two spots corresponding to phosphorus containing species.

System A.

R_F	
0.53	2-hydroxyethyl phosphonic acid
0.68	starting material

The solution was treated with HCl, filtered and concentrated by freeze-drying and chromatographed (DEAE cellulose). Elution with dilute HCl yielded a solution containing only the material of R_F 0.53 (System A). This solution was stable at room temperature indefinitely - no new phosphorus-containing components being detected chromatographically after two months.

(ii) Using excess $AgNO_3$, 0.98 gm. AgBr was collected (100%) prior to HCl treatment and subsequent work-up. This solution contained only the component of R_F 0.53.

B. Silver oxide

2-bromoethyl phosphonic acid (1.0 gm; 5.3 mmole) was dissolved in water (10 ml). To this solution were added dilute HNO_3 (3N, 5 ml) and Ag_2O (3 gm; excess). The mixture was stirred at 50°C for 14 hours and examined chromatographically (System A). Apart from a small spot due to starting material (R_F 0.68), a single component (R_F 0.53) was obtained. Treatment with HCl, filtration, concentration and chromatography on DEAE yielded a solution of this component (in dilute HCl) identical to that obtained from the $AgNO_3$ reaction.

Attempted isolation of 2-hydroxyethylphosphonic acid

Aliquots of the acidic solutions of 2-hydroxyethyl phosphonic acid were subjected to various procedures in an effort to isolate the material.

(i) Elution (H_2O) from various columns to give neutral solutions resulted in decomposition to ethylene and Pi, the former confirmed by conversion to 1,2-dibromoethane and the latter by chromatographic comparison. In the cases of DEAE and AG11A8 columns, decomposition occurred mainly on the column. With anion exchange resins the material was eluted but decomposed immediately after elution. The pH of the eluates was always between 5 and 7.

(ii) Treatment of a concentrated solution (freeze-dried) with a saturated solution of $BaCl_2$ followed by ethanol gave a white precipitate. Chromatographic analysis showed a mixture of Pi and 2-hydroxyethyl phosphonic acid in an approximate ratio of 2:3. This solid could not be purified further without decomposition.

Diazotisation of 3-aminopropyl phosphonic acid

3-aminopropyl phosphonic acid[191] (1.39 gm; 10 mmole) was dissolved in dilute HCl (0.5 N, 15 ml) and the solution cooled to 0°C, with stirring. Solid $NaNO_2$ (4 gm) was added in portions and the solution was stirred at 0°C, for 5 hours. Examination of the solution chromatographically (System A) showed a trace of starting material and a new phosphorus containing component migrating with R_F 0.60. The solution was concentrated by freeze-drying and the residue treated with saturated $Ba(OH)_2$ solution. The precipitate (1.54 gm) was collected and washed by centrifugation and, without purification, was dissolved in H_2O (5 ml) and applied to a column of Dowex 50 (Li^+) (1225 cm). Elution with H_2O and freeze-drying of the eluate gave a white amorphous powder (0.50 gm). This powder was crystallised from aqueous ethanol (inverse crystallisation) to give the dilithium salt of 3-hydroxypropyl phosphonic acid (0.37 gm).

ν (KBr pellet) ca. 1270 (s, very broad) 1100 (s) 1050 (s) 1000 (s) cm^{-1}

Diethyl 3-acetoxypropyl phosphonate was prepared from 3-bromopropyl acetate and triethyl phosphite[147] in 63% yield, having B.Pt. 76-86°C/ 0.02 - 0.05 mm (lit.[147] B.Pt. 96°/0.1 mm).

ν (liquid film) 1740 (s) 1253 (sh,s) 1235 (s) 1062 (s) 1025 (s) 960 (m/s) cm^{-1}

δ (neat) -27.8 ppm

3-hydroxypropyl phosphonic acid, dilithium salt was prepared by the method of Eberhard and Westheimer[147] in low yield (23%). Its IR was virtually identical to that of the product obtained by diazotisation of 3-aminopropyl phosphonic acid.

ENOL PHOSPHATE REARRANGEMENTS

Materials

Enol phosphates were prepared as their diethyl esters via the Perkow[106] reaction and were purified by vacuum distillation. The isomeric β-ketophosphonates were prepared either from suitable α-haloketones and triethyl phosphite via the Arbusov[100-192] reaction or by an Arbusov reaction between the cyclic ethylene acetal of a suitable α-haloketone and triethyl phosphite, followed by dilute acid cleavage and distillation. The physical constants and other relevant data are tabulated below.

Compound	Refs.	Yield	Lit. B. Pts.	B. Pt.	Purity (GLC)
A. Diethyl cyclohexenyl-phosphate	193,194	94%	140°C/2mm[193]	106-7°/ 0.04mm	99.9%
B. Diethyl 1-phenylvinyl-phosphate	195	95%	103°/ 0.005 mm	127-133°/ 0.005 mm	98.79%
C. Diethyl 1-carbethoxy-vinyl phosphate	196	65%	93°/0.05 mm	90-92°/ 0.08 mm	99.4%
D. Diethyl benzoylmethyl-phosphonate	197	40%	173°/ 2.5 mm	150-1°/ 0.4 mm	99.6%
E. Diethyl 2-oxocyclohexyl phosphonate	-	-	See footnotes		100%

Notes:-	**A.** τ **(neat)**	**4.53 (multiplet) 1H**
		5.90 (multiplet) 4H
		7.90, 8.33 (multiplets) 8H
		8.72 (triplet, J = 6.9 c/s) 3H
	δ **(neat)**	**+ 6.8 ppm**
	B. τ **(neat)**	**2.0 - 2.6 (multiplet) 5H**
		4.50 (multiplet) 2H
		5.80 (multiplet) 4H
		8.74 (triplet, J = 6.9 c/s) 6H
	δ **(neat)**	**+ 6.7 ppm**
	λ **max (EtOH)**	**208.5 (15,500), 215 (9,900),**
		245 (12,550) $m\mu$
	ν **(liquid film)**	**1740 (s) 1635 (m) 1300 (s) 1030 (s)** cm^{-1}
	τ **(neat)**	**4.1 (doublet of triplets)* 2H**
		5.8 (multiplet) 6H
		9.0 (triplet of triplets, J = 6.9 c/s) 9H

***The internal chemical shift difference (**$\Delta\tau$**) between the vinyl proton triplets was found to be markedly affected by the solvent. The** $\Delta\tau$ **values are listed below.**

Solvent	$\Delta\tau$ c/s
Neat	18.8
Acetic acid	20.9
Benzene	15.4
Carbon tetrachloride	18.5
Deuterochloroform	20.5
δ (neat)	+ 6.9 ppm

Polymerisation: On standing at room temperature for 5 days this material polymerised to a thick, pale yellow gum. At 0°C, polymerisation took several weeks.

D. τ(neat) 1.80, 2.40 (multiplets) 5H
5.85 (multiplet) 4H
8.45 (doublet, J = 16.6 c/s) 2H
8.90 (triplet, J= 7 c/s) 6H

δ(neat) -18.4 ppm

2,4-dinitrophenylhydrazone: M.Pt. 145-7°C

ν(Nujol mull) 1618 (s) 1583 (s) 1500 (m) 1240 (s) 1135 (s) 1020 (s) cm^{-1}

E. (i) This material was prepared in low yield as a 1:1 mixture of the enol phosphate and β-ketophosphonate. The phosphonate was obtained by separation on a preparative GLC (Autoprep) machine. Only sufficient material was obtained to provide a standard for GLC investigations.

(ii) An attempt to prepare this material from the ethylene acetal (1,3-dioxolane) of α-chloro-cyclohexanone and $(EtO)_3P$ at 160°C failed, the dioxolane remaining inert under these conditions[198].

Attempted rearrangements

Notes:-

(i) The experiments are described for diethyl cyclohexenyl phosphate. Experiments with other enol phosphates were identical in most respects except the results, which are tabulated at the end of this sub-section.

(ii) Irradiation (Medium pressure Hg lamp; quartz probe) and thermal experiments were followed by IR and GLC. The residues from these experiments were examined by ^{31}P NMR. The limits of resolution are estimated as: GLC $\pm$ 0.5%; ^{31}P NMR $\pm$ 4%

(iii) Retention times appeared to vary depending upon the age of the column packing; they are therefore not quoted. All comparisons with standards were made with consecutive runs.

(a) Diethyl cyclohexenyl phosphate (1.0 gm) was maintained at 200°C in an open tube under an atmosphere of N_2. No changes occurred in the GLC trace during 20 minutes, whereafter rapid

decomposition occurred.

(b) Diethyl cyclohexenyl phosphate (1.0 gm) was dissolved in dry xylene (10 ml) and the solution heated under reflux. Daily GLC examination showed the appearance of diethyl 2-oxocyclohexyl phosphonate (0.5% after 1 day, 0.7% after 2 days, 0.7% after 3 days). The solution was heated for a total of 8 days without further change occurring.

(c) Diethyl cyclohexenyl phosphate (0.5 gm) was placed in a stoppered quartz flask under dry N_2. The flask was placed out of doors, in sunlight, for 6 weeks. Apart from a slight colouration developing, no isomer was detected by GLC or ^{31}P NMR.

(d) Diethyl cyclohexenyl phosphate (1.0 gm) was dissolved in cyclohexane (Spectrosol, 300 ml), the solution degassed and stirred under dry N_2 whilst being irradiated for 40 hours, during which time no changes occurred. Evaporation of the solvent and examination of the residue by ^{31}P NMR failed to reveal any phosphonate. Iterative scanning also failed to disclose any phosphonate.

(e) The photolysis experiment (d) was repeated using (i) dioxan and (ii) ethanol as solvents. In dioxan, no measureable changes occurred other than slow darkening of the solution and deposition of polymeric material on the probe. In ethanol, IR examination showed the rapid appearance (< 30 mins) of a carbonyl absorption. (ν = 1720 cm^{-1}). Examination by GLC showed this to be due to cyclohexanone, presumably formed by a photo-induced solvolysis reaction. The appearance of carbonyl absorption was accompanied by a corresponding diminution in the intensity of the ν c=c absorption.

(f) Diethyl cyclohexenyl phosphate (0.5 ml) was treated with boron trifluoride:acetic acid complex (0.5 ml) and the solution stored at room temperature. Within 5 hours, a phosphonate peak (0.5%) had appeared in the GLC trace. No change occurred thereafter up to 25 hours. This result could not be confirmed by ^{31}P NMR.

(g) Diethyl cyclohexenyl phosphate (0.5 ml) was treated with boron trifluoride diethyl etherate (0.5 ml). GLC examination revealed no changes after 20 hours at room temperature.

(h) Diethyl cyclohexenyl phosphate (0.5 ml) was dissolved in glacial acetic acid (3 ml). On standing at room temperature, no changes were detectable after 20 hours. The solution was heated to 50°C for a further 5 hours without detectable change.

(i) Diethyl cyclohexenyl phosphate (0.5 ml) was treated with a solution of p-toluenesulphonic acid (50 mgm) in benzene (3 ml). This solution remained unchanged after 3 days at room temperature.

(j) Diethyl cyclohexenyl phosphate (1.0 gm; 4.3 mmole) was dissolved in xylene (3 ml). To this solution was added 2-chlorocyclohexanone (0.57 gm; 4.3 mmole) and the solution boiled under reflux for 8 days. No change was detectable by GLC or IR.

(k) Diethyl cyclohexenyl phosphate (1.0 gm; 4.3 mmole) was dissolved in cyclohexane (Spectrosol, 300 ml) and the solution treated with 2-chlorocyclohexanone (0.57 gm; 4.3 mmole). The solution was photolysed for 48 hours without detectable appearance of phosphonate.

Tabulated results

Enol phosphate	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)	(j)	(k)
Diethyl cyclohexenyl phosphate	-	+	-	-	-	-	-	-	-	-	-
Diethyl 1-phenylvinyl phosphate	-	+	0	+	-	-	-	+	-	+	+
Diethyl-1-carbethoxyvinyl phosphate	-	-	0	-	-	-	-	+?	-	0	0

+ = appearance (never >3%) of β-keto phosphonate

- = no observed change, other than decomposition

0 = experiment not performed.

THE PERKOW REACTION

A. Perkow reactions in the presence of alcohols

The appropriate phenacyl halide (10 mmole) was treated with the trialkyl phosphite (20 mmole) and, where appropriate, the corresponding alcohol (20 ml, MeOH for $(MeO)_3P$ reactions and EtOH for $(EtO)_3P$ reactions). The neat reactions were maintained at 120°C for 30 mins.; those carried out in solution were kept in a 120 °C oil bath for 30 mins. The reaction residues were examined by ^1H and ^{31}P NMR, an analysis of the proportions of enol phosphate and β-ketophosphonate as well as of dehalogenated ketone, unreacted starting materials or other products being carried out. In some cases, the greater complexity of the proton spectra precluded a reliable analysis; in these cases greater weight, regarding the proportions of enol phosphate and β-ketophosphonate, was given to the ^{31}P measurements. All spectra were run in duplicate and a mean value of the integrated areas taken. The integration was checked, where possible, by cutting out the appropriate peaks and weighing them. The estimated experimental error is $\pm$ 2%.

These results are gathered in Table VI.

TABLE VI

Reaction	Enol Phosphate (%)		β-ketophosphonate (%)		Other (%)
	^{31}P	^{1}H	^{31}P	^{1}H	
$(MeO)_3P$, $PhCOCH_2Cl$	94.6	92.0	5.4	8.0	
$(MeO)_3P$, $PhCOCH_2Cl$, MeOH	63.0	58.0	10.0	11.5	(a) 27.3
$(EtO)_3P$, $PhCOCH_2Cl$	87.9	86.2	12.1	13.8	
$(EtO)_3P$, $PhCOCH_2Cl$, EtOH	93.5	95.4	6.5	4.6	
$(MeO)_3P$, $PhCOCH_2$ Br	19.0	20.0	69.9	64.0	(b) 10.3
$(MeO)_3P$, $PhCOCH_2$ Br, MeOH	66.4	59.3	13.8	13.3	(a) 11.4
					(b) 5.0
$(EtO)_3P$, $PhCOCH_2$ Br	21.3	18.1	73.7	72.3	(a) 6.4
					(d) 5.0
$(EtO)_3P$, $PhCOCH_2$ Br, EtOH	71.3	58.0	17.5	10.8	(d) 11.2

(a) α-hydroxyphosphonate

(b) dehalogenated ketone

(c) unreacted haloketone

(d) "other" phosphate, probably partly hydrolysed since chemical shifts were 0 ± 1 ppm

The $\Delta\tau$ values of the vinyl proton triplets of both dimethyl and diethyl 1-phenylvinyl phosphate were measured and found to vary in much the same way as the $\Delta\tau$ values of diethyl 1-carbethoxyvinyl phosphate.

Ester	Solvent	$\Delta\tau$ c/s
Dimethyl	None	10.9
Dimethyl	MeOH	12.5
Diethyl	None	5.0
Diethyl	EtOH	6.0

B. Intermediates in the Perkow reaction

Materials and conditions

Chloral was redistilled from molecular sieves before use and stored over molecular sieves, under an atmosphere of dry N_2. All recrystallisations were carried out in a dry-box in an atmosphere of dry nitrogen. All solvents were redistilled and stored over molecular sieves under a nitrogen atmosphere. Melting points were measured in sealed capillaries.

Ethylene phosphorochloridite was prepared by the procedure of Lucas and co-workers[199] in 85% yield, having B.Pt. 54°C/22 mm. (lit.[199] B.Pts. 62°/35 mm; 54°/25 mm).

ν (liquid film) 2980, 2910 (m) 1470 (m) 1210 (m) 1005 (s) 922 (s) 807 (s) 761 (s) 600 (s) 445 (s) cm^{-1}

δ (neat) −169.0 ppm (lit. −166.6[200]; −167[201]; −168.4[202] ppm)

Ethylene methyl phosphite was prepared by the Lucas[199] procedure from ethylene phosphorochloridite and methanol in 80% yield, having B.Pt. 43-4°/20 mm. (lit.[199] B.Pts. 68°/47 mm; 41.5°/10 mm; 56°/25 mm).

ν (liquid film) 2980 (s) 2950,2910,2840,(s) 1460 (m) 1040,1010 (s) 922 (s) 795 (m) 772 (s) 725 (s) 610 (s) cm^{-1}

δ (neat) −131.7 ppm (lit. −132.4[203]; −131.6[204] ppm)

Reaction between chloral and ethylene methyl phosphite

Ethylene methyl phosphite (8.524 gm; 69.9 mmole) was added dropwise to stirred, cooled chloral (20.5 gm; 13.5 ml, 139.8 mmole, 2.0 equiv). Cooling was such that the internal temperature did not exceed 50°C. After addition, petroleum ether (boiling range 60-80°C, 50 ml) was added to the semi-solid mixture, causing complete solidification. The solid was broken up with a spatula and the slurry stirred magnetically for 30 minutes to produce a fine crystalline powder. This material was collected, washed with petroleum ether and dried *in vacuo* over fresh P_2O_5, yielding 26.3 gm (93%) of material having M.Pt. 95-8°C (142°dec).

Analysis

$C_7H_9Cl_6O_5P$ requires C,20.15; H,2.16; Cl,51.10; P,7.43%

found C,19.72; H,2.18; Cl,48.19; P,8.61%

Note:- Sample was heated in vacuo before analysis, undoubtedly causing some decomposition and loss of volatile products thereof (chloral). The analytical discrepancy between the P and Cl analyses are internally consistent, indicating an extent of 26% decomposition.

δ (CCl_4) Initially: δ = + 27, + 21 ppm

After 30 mins.: δ = + 27, + 21, + 6.9 ppm

+ 27 peak composed of two peaks in ratio 3:2, at + 36.0, + 28.0ppm

+ 21 peak symmetrical.

The material which crystallised from a cooled solution in CCl_4 (previously used for NMR measurements) was dissolved in pre-heated CCl_4 and a spectrum run immediately. Thereafter, spectra were run at intervals, the results of which are tabulated below.

Time (minutes)	% due to peaks at:-		
	+ 6.9	+ 21.0	+ 27.0 ppm
"0"	0	95	5
5	0	80	20
10	5	70	25
15	10	65	25
30	25	35	40
180	50	25	25
1440	55	24	21

Estimated accuracy ± 5%

τ (CCl_4, fresh solution) 2.68 - 2.85 (multiplet) 1H

4.10 - 4.40 (multiplet) 1H

*5.31 - 6.35 (multiplet) 7H

* Partially resolved doublet, J_{PH}= 12.5 c/s at higher resolution.

ν (Nujol mull) 1055 (s, broad) 825 (s, broad) 730 (s) 640 (m) 445 (m) cm^{-1}

Mass spectrum m/e

M^+ 413.8229

Base peak: 139

$(m^*)^+$ 297, (414 → 349)

109 (268 → 171)

$C_7H_9{}^{35}Cl_6O_5P$ requires: 413.8318

See Appendix I for a discussion of the NMR observations and Appendix II for a discussion of the mass spectral behaviour of this and related compounds.

Thermal decomposition of the chloral:ethylene methyl phosphite adduct

The 2:1 adduct (9.7 gm; 23.25 mmole) was heated in a flask, under a stream of dry N_2 to 140-180°C. The N_2 stream was passed through an ice-cooled trap to permit collection of the volatile products. The pyrolysis was continued for 65 minutes. Two products were obtained; a pungent-smelling colourless liquid (3.31 gm; 97%) having B.Pt. 98-9°C/760 mm., and a residue (6.38 gm) which was distilled *in vacuo* to give a colourless liquid (5.35 gm) having B.Pt. 110-20°C/0.5 mm. (86%). Yields are based on structure assignments.

(i) Volatile product. Infrared spectrum identical to that of a sample of chloral.

(ii) Distilled residue.

ν (liquid film) 3080, 2965, 2863 (m) 1650 (m) 1285 (s, broad) 1030-60 (s), 1080 (s, broad) 855 (m) 820 (m) 750 (s) 665 (s) cm^{-1}

τ (CCl_4) 2.84 (doublet, J_{PH} = 6.0 c/s) 1H

5.58 (doublet of triplets, J_{PH} = 9.0 c/s, J_{HH} = 5.5 c/s) 2H

6.05 (doublet, J_{PH} = 12.2 c/s) 3H

6.22 (triplet,, J_{HH} = 5.5 c/s) 2H

δ (neat) + 7.1 ppm

On standing at room temperature, the ^1H spectrum gradually became more complex but with little change occurring in the positions of absorption. The major effect was the appearance of peaks (with the same coupling constants) very slightly upfield of the original peaks. This was interpreted as showing that another isomer was being formed - presumably a geometrical isomer since the integrated areas of the absorption bands remained in a 1:2:3:2 ratio.

Mass spectrum m/e

M^+ 267.9223

$C_5H_8{}^{35}Cl_3O_4P$

requires 267.9225

Base peak 109 or 157 (intensity variation in successive spectra)

$(m^*)^+$ 109 (268 → 171)

(see Appendix II)

<u>o-phenylene phosphoro chloridite</u> was prepared by the procedure

of Anschütz[205] in 90% yield, having B.Pt. 90-1°/15 mm. (lit.[205] B.Pt. 85°/14 mm)

τ (neat) 2.88 (complex multiplet)

δ (neat) -174.2 ppm (lit[206] -173.0 ± 2 ppm)

Methyl o-phenylenephosphite

o-phenylene phosphorochloridite (87.25 gm; 0.5 mole) was dissolved in dry ether (1 litre), and the solution treated consecutively with freshly activated molecular sieves (10 gm) and triethylamine (50.5 gm; 0.5 mole). The solution was stirred and cooled to -10°C, moisture being excluded, during the addition, over 30 mins., of methanol (16 gm, 0.5 mole). After addition, the solution was stirred at room temperature for 2 hours, filtered rapidly through a bed of celite and the filtrate evaporated to yield a colourless liquid.

Vacuum distillation gave methyl o-phenylene phosphite (73.5 gm. 86%) having B.Pt. 48°/0.8 mm. (lit.[164] B.Pt. 76-7°/15 mm).

ν (liquid film) 3070, 3000, 2950, 2840 (w-m)
1477 (s) 1370 (m) 1230 (s) 1020 (s)
825 (s) 740 (s) cm^{-1}

τ (neat) 2.89 (complex multiplet) 4H
6.80 (doublet, J_{PH} = 8.5 c/s) 3H

δ (neat) -126.5 ppm

Reaction between methyl o-phenylene phosphite and chloral

Methyl o-phenylene phosphite (3.40 gm. 20 mmole) was treated with chloral (15 ml, excess) and the solution boiled under reflux for 2 hours. NMR examination of the solution showed, apart from starting phosphite, two phosphorus containing species in solution, with approximate values + 22 and + 25 ppm.

Treatment of this solution with petroleum ether (boiling range 60-80°C, 50 ml) caused precipitation of a crystalline white solid. The supernatant solution was decanted, more petroleum ether (50 ml) added to the solid and the mixture heated to reflux (maintaining, at all times, an atmosphere of dry N_2). On cooling, an oil separated. The supernatant solution was decanted into a separate flask, whereupon crystals were rapidly deposited. After chilling to 0°C the product was collected, washed with a little cold petroleum ether and dried in vacuo to yield the 2:1 adduct (4.73 gm., 75%), having m.Pt. 142-9°C (slow decomposition at the melting point).

ν (Nujol mull) 1630 (m) 1600 (m) 1485 (m) 1353 (m) 1256 (m) 1185 (s) 1072, 1055 (s) 902 (m) 850 (m) 820 (m) 730 (m) 635 (s) cm^{-1}

τ ($CDCl_3$)	2.85 (multiplet)	4H
Fresh	4.59 (singlet)	1H
solution	4.95 (doublet, J = 1.5 c/s)	1H
	6.15 (doublet, J_{PH} = 14.0 c/s)	3H

After standing for a further 10 minutes, the following new absorptions had appeared.

4.40 (singlet?) possibly a doublet with J = 11.8 c/s, one half obscured by the peak at 4.59

5.30 (doublet, J = 2.2 c/s)

6.01 (doublet, J = 15.0 c/s)

For a discussion of these results and structural assignments arising therefrom see Appendix I.

δ (C_6H_6 or $CHCl_3$) A sample of the 2:1 adduct was crystallised from CCl_4 and the crystalline solid dissolved in preheated C_6H_6 or $CHCl_3$ (same result) the ^{31}P NMR spectrum being measured immediately.

Time (mins.)	δ (ppm)
0	+ 22.2 (only peak)
15	+ 22.2: + 33.1 (5:1)

The peak at + 22.2 ppm slowly became unsymmetrical and a peak to higher field began to appear. After t = 120 mins., a measurement revealed:

δ = + 22.2; + 23.4 ppm (Ratio 2:3) and + 33.1 ppm

See Appendix I

Mass spectrum	m/e
M^+	461.8324
$C_{11}H_9{}^{35}Cl_6O_5P$ requires	461.8318
Base peak	186

The 2:1 adduct was also formed by (i) an interaction between excess chloral and methyl o-phenylene phosphite at room temperature. After 12 days, crystallisation began and was complete after 5 weeks.

(ii) reaction between the phosphite and chloral (equimolar proportions) in benzene at reflux for 3 days. After removal of the solvent the residue was crystallised from CCl_4 or petroleum ether.

Pyrolysis of the 2:1 chloral: o-phenylene phosphite adduct

(i) The 2:1 adduct (0.5931 gm; 1.279 mmole) was heated at 182°C in vacuo (0.005 mm). The products of decomposition were passed successively through an

ice-cooled and a liquid nitrogen cooled trap. Under these conditions the adduct partly evaporated and recondensed on the cold connecting arm (0.483 gm) and partly decomposed to chloral (0.0693 gm., 36%) and, presumably, to chloromethane (collected in the nitrogen cooled trap, the contents of which evaporated when the temperature was allowed to rise). The "condensed adduct" was examined by IR spectroscopy.

ν (nujol mull) 1630 (w) 1490 (s) 1355 (m) 1260 (s) 1190 (s) 1060, 1075 (s) 905 (s) 820, 853 (s) 733 (s) 660 (s) cm^{-1}

This spectrum is virtually identical to that recorded for the pure 2:1 adduct.

(ii) The 2:1 adduct (0.731 gm; 1.575 mmole) was heated to 190°C at atmospheric pressure whilst a stream of nitrogen was passed through the liquid. The gas stream was subsequently passed through a trap cooled by ice. The flask residue slowly darkened and pyrolysis was stopped after 35 minutes. Chloral (0.221 gm; 1.510 mmole, 96%) was collected as the sole trap component (identified by comparison with a standard IR spectrum).

The flask residue, which smelt strongly of catechol, was examined by IR spectroscopy, but exhibited only very broad absorptions throughout the spectrum.

Intermediates with acyclic phosphites

Reaction between triethyl phosphite and chloroacetone

Chloroacetone (9.25 gm; 0.1 mole) was cooled to -33°C and stirred at this temperature during the dropwise addition of triethyl phosphite (8.3 gm; 0.05 mole). The colourless solution was examined immediately after the addition (at 33°C, NMR cavity temperature).

δ (neat)	+ 8.3 ppm	+ 47 ppm
Ratio	19 :	1

The high field peak disappeared very rapidly (~5 minutes) and could not be detected using the computer of average transients (C.A.T.).

When this reaction was carried out using equimolar proportions of chloroacetone and triethyl phosphite the same result was obtained.

Reaction between triethyl phosphite and bromoacetone

Bromoacetone (13.7 gm; 0.1 mole) was cooled to -20°C and stirred at this temperature during the dropwise addition of triethyl phosphite (8.3 gm: 0.05 mole). Rapid examination of the solution by ^{31}P NMR showed a single peak at + 10.8 ppm. No trace of a higher field absorption could be detected.

Reaction between triphenyl phosphite and chloral

(i) Triphenyl phosphite (6.20 mmole) was mixed with chloral (30 ml; excess) and the solution boiled under reflux for 5 hours. Hourly sampling and examination by ^{31}P NMR gave the following result.

t (hours)	δ (ppm)
0	-127.5
1	-127.5 + 20.2 + 53.5?
2	-127.5 + 20.2 + 53.5 + 56.2?
3	-127.5 + 20.2 + 53.5 + 56.2
4	- + 20.2 + 53.5 + 56.2
5	- + 20.2 + 53.5 + 56.2

(ii) The same proportions of reactants were mixed and stirred at room temperature for 4 weeks. An amorphous solid which began to separate after 5 days, was collected, washed with benzene and dried to give 7.35 gm. of material having an indeterminate decomposition point above about 280°C. This material was insufficiently soluble in suitable solvents to obtain any NMR spectra.

ν (Nujol mull) 1591 (w) 1491 (m) 1325 (m) 1120 (s) 1085 (s) 1030 (m) 970 (v.s.) 842 (s) 800 (s) 672 (s) cm^{-1}

Mass spectrum	m/e
M^+	indeterminate
Highest mass peak	455?
Base peak	82

The fragmentation pattern is discussed in Appendix II.

Phosphite/carbonyl reactions in the presence of acids

The reaction of benzil with trimethyl phosphite in the presence of acetic acid

Benzil (2.10 gm; 10 mmole) was dissolved in $CHCl_3$ (20 ml) and to this solution was added glacial acetic acid (1.2 gm: 20 mmole). Whilst stirring under an atmosphere of N_2, trimethyl phosphite (1.24 gm; 10 mmole) was added, causing an increase in temperature. After addition, the almost colourless solution was examined by NMR.

δ = + 1.3 ppm (only peak)

Thin-layer chromatography of the solution (silica gel; hexane:chloroform, 9:1) showed a trace of unreacted benzil (R_F 0.52), a major component with R_F 0.025 and a trace of material (R_F 0.11).

Evaporation of the solution gave an oil which slowly crystallised, producing dimethyl 1-benzoylbenzyl phosphate (2.0 gm; 62%) having M.Pt. 69-70°C.

The residue was dissolved in ether and the solution treated with petroleum ether to give a second crop (0.87 gm; 27%) having M.Pt. 69-70°C. Total yield = 89%.

(lit.[125] M.Pt. 78°C)

Chromatography:	R_F 0.87 (System B), giving an immediate yellow colour with Ehrlich-Isherwood spray reagent.
ν (Nujol mull)	1700 (s) 1278 (s) 1086, 1060, 1040 (s, broad) cm^{-1}
τ ($CDCl_3$)	1.83 (multiplet) 2H
	2.38 (multiplet) 8H
	3.13 (doublet, J_{PH} = 8.0 c/s) 1H
	6.16 (doublet, J_{PH} = 11.6 c/s) 3H
	6.42 (doublet, J_{PH} = 11.6 c/s) 3H
δ ($CHCl_3$)	+ 0.8 ppm (lit.[202] 0.0 ppm)
Mass spectrum	m/e
M^+	320.0815
$C_{16}H_{17}O_5P$ requires	320.0813
Base peak	105
$(m^*)^+$	143 (320 → 215)

The reaction of biacetyl with trimethyl phosphite in the presence of acetic acid

Biacetyl (8.6 gm; 0.1 mole) in CCl_4 (20 ml) was treated with glacial acetic acid (12 gm; 0.2 mole) and the solution stirred at room temperature under N_2. Trimethyl phosphite (12.4 gm; 0.1 mole) was added in 1 ml portions during which the temperature rose to 40°C and most of the colour was discharged. After a further 5 minutes stirring, the colourless solution was evaporated to leave an oil. Vacuum distillation of the oil gave dimethyl 1-acetylethyl phosphate (16.5 gm; 84%) having B.Pt. 73-4°/0.2 mm. (lit.[114] B.Pt. 132-3°/15 mm).

Chromatography: R_F 0.88 (System B)

ν (liquid film) 2960 (s) 1725 (s) 1430 (s, broad)
1275 (s, broad) 1188 (m) 1040 (s, broad)
845 (s) 760 (m) cm^{-1}

τ (neat) 5.10 (doublet of quartets, J_{PH} = 8.1 c/s
J_{HH} = 7.6 c/s) 1H
6.12 (doublet, J_{PH} = 12.0 c/s) 3H
6.18 (doublet, J_{PH} = 12.0 c/s) 3H
7.76 (singlet) 3H
8.53 (doublet, J_{HH} = 7.0 c/s) 3H

δ (neat) -1.0 c/s (lit.[202] 0.0 ppm)

Reaction between phenacyl chloride and trimethyl phosphite in the presence of hydrogen chloride

Phenacyl chloride (15.45 gm; 0.1 mole) was dissolved in CH_2Cl_2 (50 ml). Hydrogen chloride gas was passed through the solution until saturated. Trimethyl phosphite (12.4 gm; 0.1 mole) was added in one portion, with magnetic stirring. The solution just boiled under reflux, was stirred for a further 5 minutes and evaporated. The residual, highly lachrymatory oil was dissolved in benzene (10 ml), the solution diluted with petroleum ether (boiling range 60-80°C, 20 ml), cooled to 0°C and stored overnight at this temperature. The crystalline product was collected, washed with cold petroleum ether and dried, yielding dimethyl α-hydroxy-α-chloromethyl benzyl phosphonate (3.95 gm; 15.0%) having M.Pt. 147-8°C (lit.[120] M.Pt. 144-6°C).

τ ($CDCl_3$)	2.40 (multiplet)	5H
	5.67 (singlet)	1H
	5.90 (doublet, J_{PH} = 14.0 c/s)	2H
	6.18 (doublet, J_{PH} = 10.5 c/s)	3H
	6.42 (doublet, J_{PH} = 10.5 c/s)	3H
δ ($CHCl_3$)	-20.3 ppm	

Evaporation of the mother liquors gave a colourless oil, which on vacuum distillation gave:-

(i) Phenacyl chloride (7.5 gm; 48.5%) having B.Pt. 80-2°/0.5 mm and M.Pt. 55-6°C. IR spectrum identical to that of a standard.

(ii) Dimethyl 1-phenylvinyl phosphate (5.76 gm; 25.3%) having B.Pt. 131-3°/0.05 mm (lit.[120] B.Pt.112-4°/0.01 mm).

ν (liquid film) 3060 (w) 2960, 2860 (m) 1640 (m-s) 1275 (s,broad) 1190 (m) 1050 (s, broad) 850 (s) 770 (s) 703 (m-s) 690 (m) cm^{-1}

τ (neat) 2.40 (multiplet) 5H

4.68 (doublet of triplets, J_{PH} = 5.0 c/s, J_{HH} = 2.0 c/s) 2H

6.15 (doublet, J_{PH} = 12.6 c/s) 6H

δ (neat) + 6.5 ppm

2-oxo phosphonium compounds

Reaction between triphenyl phosphine and phenacyl bromide

Phenacyl bromide (1.99 gm; 10 mmole) was dissolved in chloroform (5 ml) and to the stirred solution was added triphenyl phosphine (2.62 gm; 10 mmole) in chloroform (5 ml). An exothermic reaction ensued, the solution becoming yellow. After 30 minutes, the solution was evaporated and the residual white solid recrystallised from water to give phenacyl triphenyl phosphonium bromide (4.1 gm; 89%) having M.Pt. 268-9°C (lit.[217] M.Pt. 269-71°C).

ν (Nujol mull) 1660 (s) 1485 (m) 1450, 1442, 1438 (s) 1208 (m) 1185 (m) 1110 (s) 993 (m) 749 (s) 715 (s) 681 (s) cm^{-1}

τ (TFA) 2.08 (complex multiplet) 20H

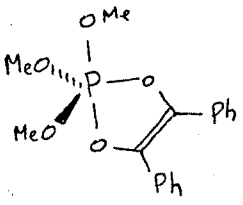
4.57 (doublet, J_{PH} = 13.0 c/s) 2H

Triphenyl phosphine benzoylmethylene was prepared from phenacyl-triphenyl phosphonium bromide by the method of Ramirez[217], in 80% yield, having M.Pt. 178-9°C (lit.[217] M.Pt. 178-80°C).

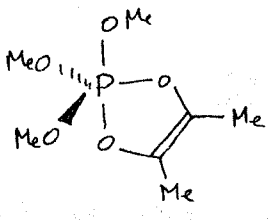
τ ($CDCl_3$) 2.2 (complex multiplet) 20H

5.45 (doublet, J_{PH} = 25.5 c/s) 1H

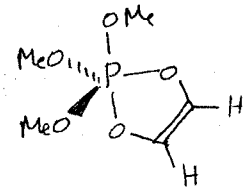
δ ($CHCl_3$) -15.6 ppm



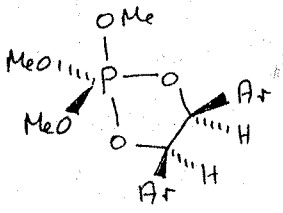
$\delta = +53$



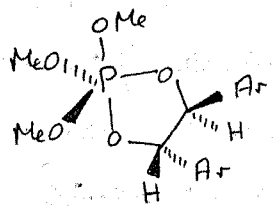
$\delta = +53$



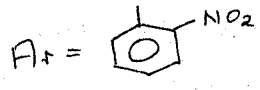
$\delta = +44.2$

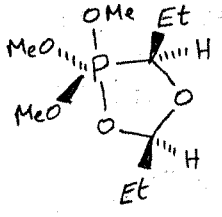


$\delta = +49.6$

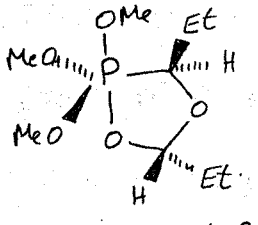


$\delta = +50.2$

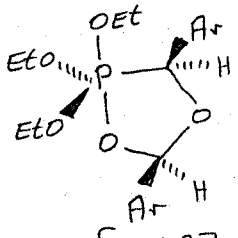




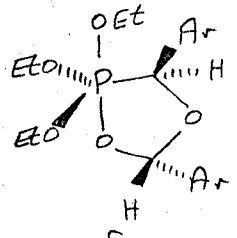
$\delta = +32.8$



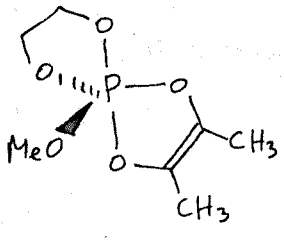
$\delta = +34.2$



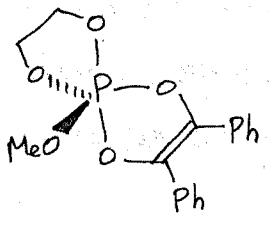
$\delta = +37$



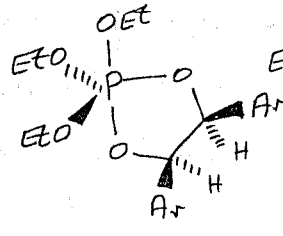
$\delta = +42$



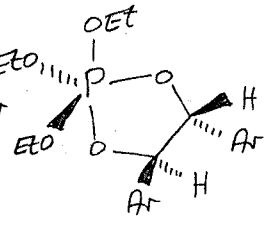
$\delta = +27.0$



$\delta = +28.1$



$\delta = +50$



$\delta = +54$

FIGURE LV

APPENDIX I

Nuclear magnetic resonance of Perkow reaction intermediates

Ramirez' work[134] has shown that 1,4,2-tetraoxyalkyl phosphoranes absorb at lower field (^{31}P) than the corresponding pentaoxyphosphoranes. Similarly, his results[133] with cis and trans isomerism about the 5-membered rings of such compounds provide a basis for assigning the isomers encountered in the work described in this thesis. Figure (LV) outlines the type of chemical shift to be expected for typical compounds and the change in chemical shift values to be expected between isomers.

The following generalisations can be drawn from Figure LV.

(i) $\Delta\delta$ (unsaturated → saturated ring) is small and negative (0 to -3 ppm)

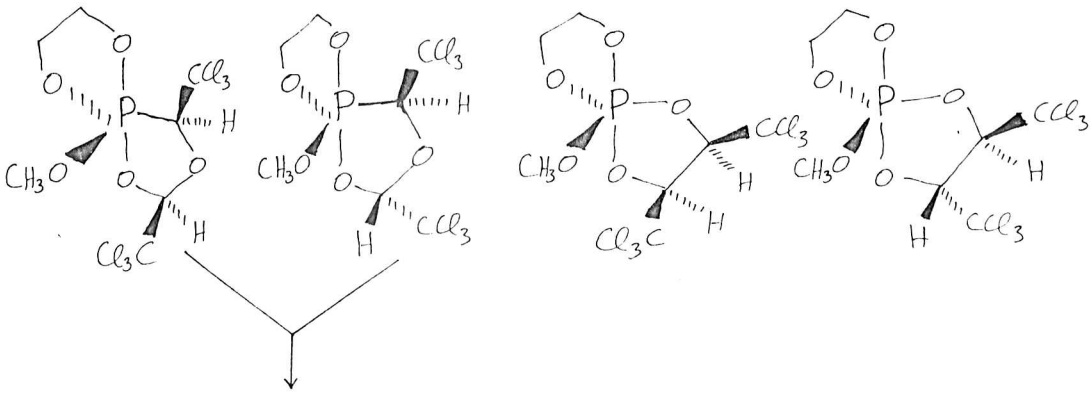
(ii) $\Delta\delta$ (cis → trans) is small and positive (+1 to +5 ppm)

(iii) $\Delta\delta$ (P in one 5-membered ring → P in two 5-membered rings, surrounded by 5 oxygen atoms in both cases) is large and negative (-20 to -25 ppm)

(iv) $\Delta\delta$ (1,4,2-tetraoxyalkyl---> 1,3,2-pentaoxy-phosphorane) is intermediate and positive (+8 to +16 ppm)

On this basis it can be reasoned that the peaks obtained from a compound such as the 2:1 chloral:ethylene methyl phosphite adduct would be in the relative order:-

Low field High field



Observed δ (ppm) + 21.0 + 26.0 + 28.0

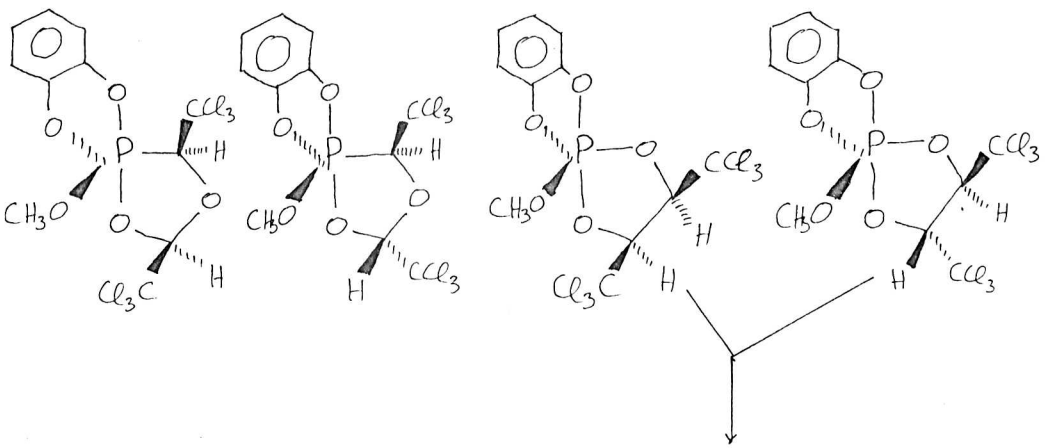
The lower field absorption (+21.0 ppm) was seen to be a symmetrical peak. This can be interpreted in two ways:

Either (i) the signal is due to a single stereoisomer

or

(ii) the signals due to the cis and trans isomers coincide.

Similar reasoning has been applied to the 2:1 chloral: o-phenylene phosphite adduct, as shown below accompanied by the observed signals.



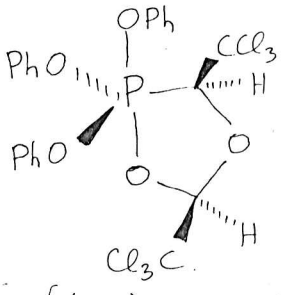
Observed δ (ppm) + 22.2 + 23.4 + 33.1

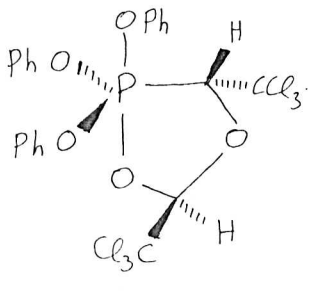
In this case the signals due to the 1,3,2-pentaoxy-phosphorane isomers would appear to coincide.

The triphenyl phosphite:chloral adduct is less easy to interpret in this manner but the signal separation (2.7 ppm) is of the order expected for cis and trans isomers. The chemical shifts of other adducts of triphenyl phosphite with carbonyl compounds[134] are shown below.

Adduct		δ (ppm	
$(PhO)_3P$:Biacetyl (1:1)		+64.7	All formulated[134] as pentaoxyphosphoranes.
$(PhO)_3P$:Biacetyl (2:1)	trans	+66.1	
$(PhO)_3P$:Biacetyl (2:1)	cis	+65.3	

In view of this data the signals observed are assigned to the 1,4,2-tetraoxyalkyl phosphorane isomers:-





Observed δ (ppm) + 53.5 + 56.2

Triphenyl phosphine benzoyl methylene

Studies of phosphine methylenes[212,219,220] have shown that:

(i) Rotation about the HC–R bond in Ph_3P–CH–R systems leads to an apparent reduction in J_{PH} eventually leading to coalescence at elevated temperatures.

(ii) The higher the coalescence temperature, the greater the barrier to rotation.

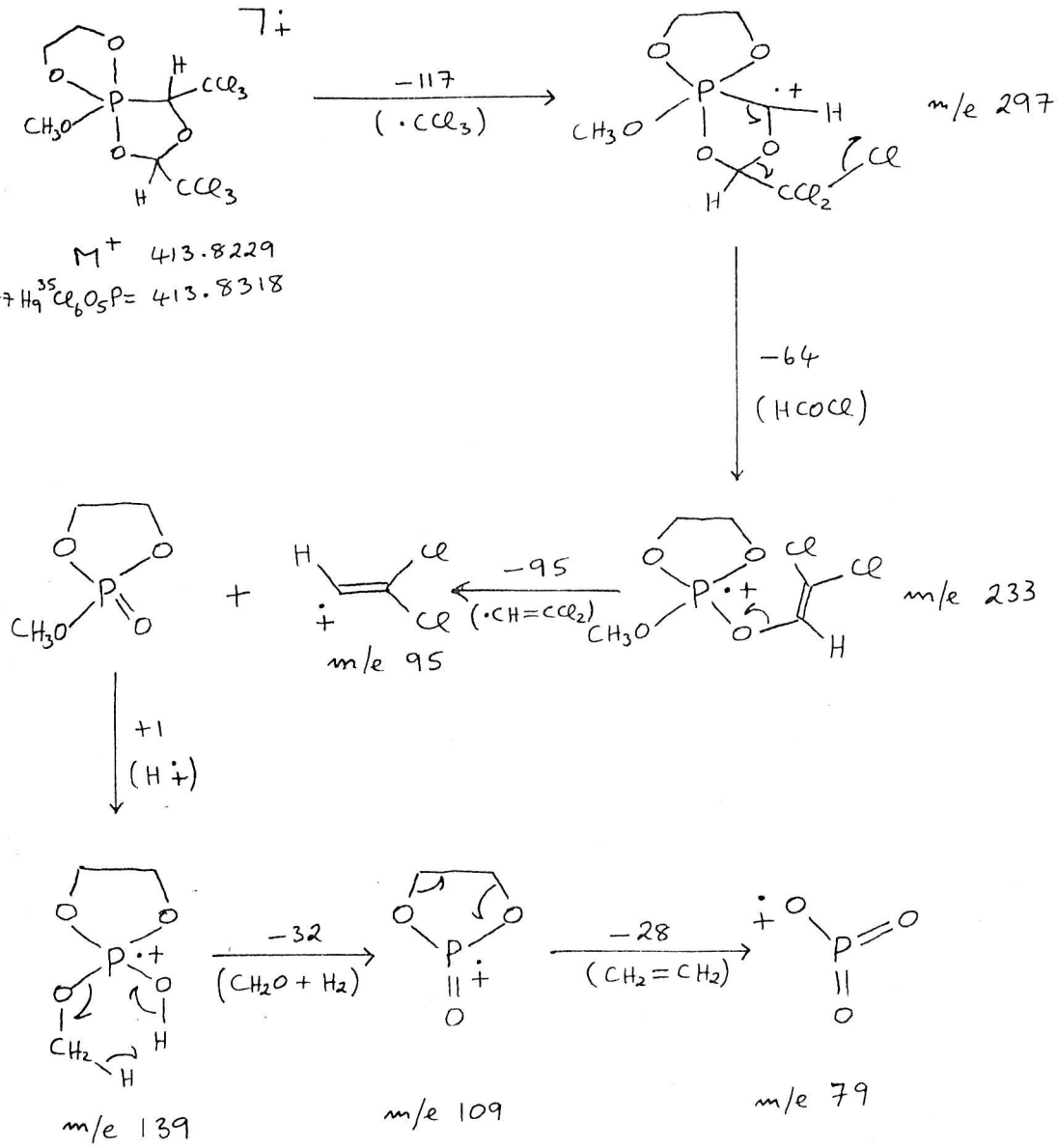
Triphenyl phosphine benzoyl methylene (τ_H = 5.45 , J_{PH} = 25.5 c/s at 33°C) exists mainly as the non-rotating conformer, an occurrence probably due to interaction between P^+ and $-O^-$.

APPENDIX II

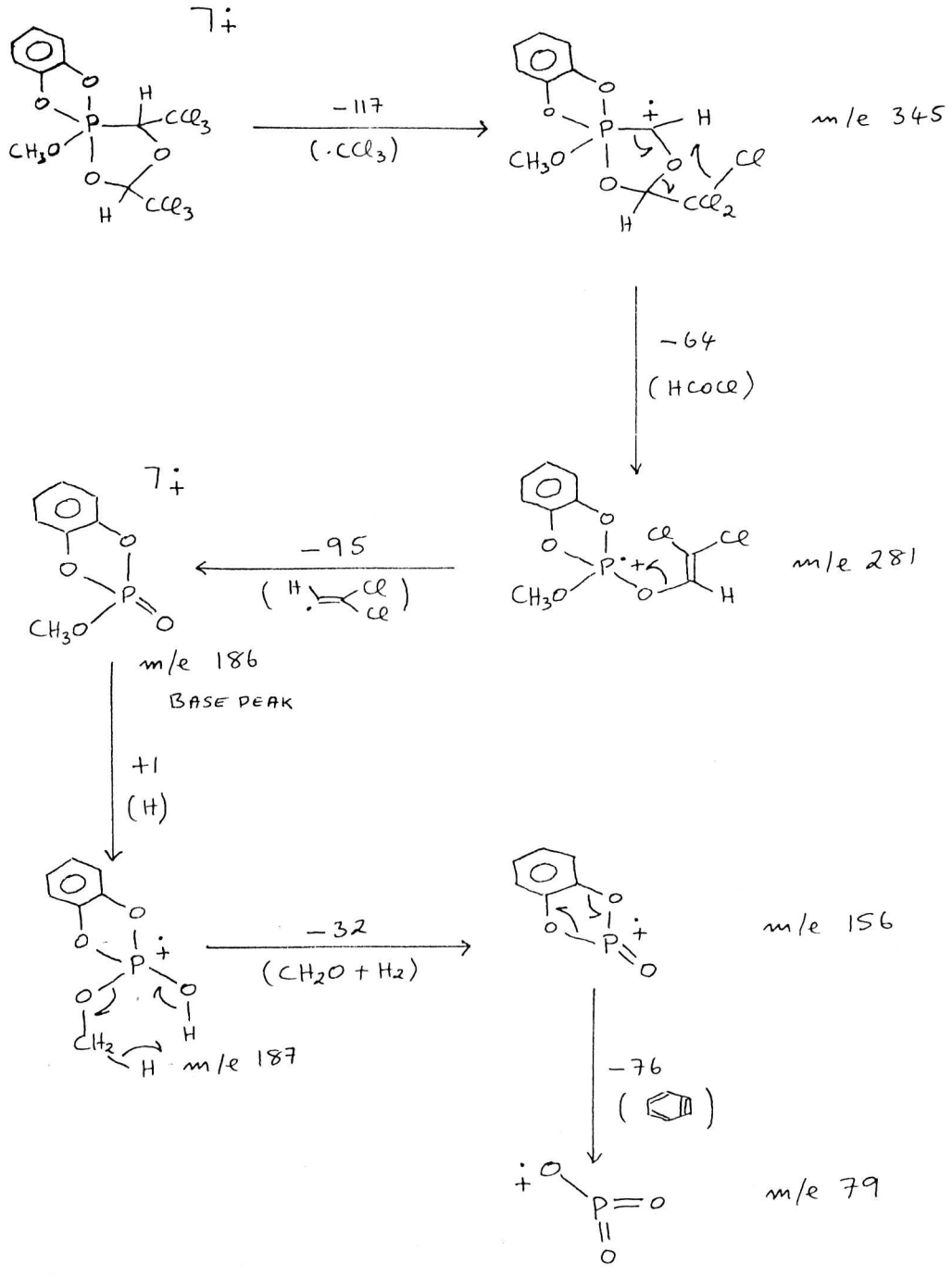
Mass spectrometry of Perkow reaction intermediates and related compounds

Little is known of the behaviour of tetraoxyalkyl phosphoranes or pentaoxyphosphoranes in the mass spectrometer[211]. Because of this, it is not possible unequivocally to assign the fragmentations observed. The assumption has been made that the crystalline samples sent for mass spectrometric analysis were largely the tetraoxyalkyl phosphorane (based on the NMR results), on which basis the fragmentation schemes have been drawn up. Though this may be the case, isomerisation will undoubtedly have occurred at the inlet temperature of the mass spectrometer. A great measure of assistance is provided by the isotopic ratio of ^{35}Cl and ^{37}Cl and the resulting ratios of m: (m+2):(m+4) etc., in polychloro-compounds[210]. The schemes presented, where appropriate, are in complete agreement with the expected isotopic ratios.

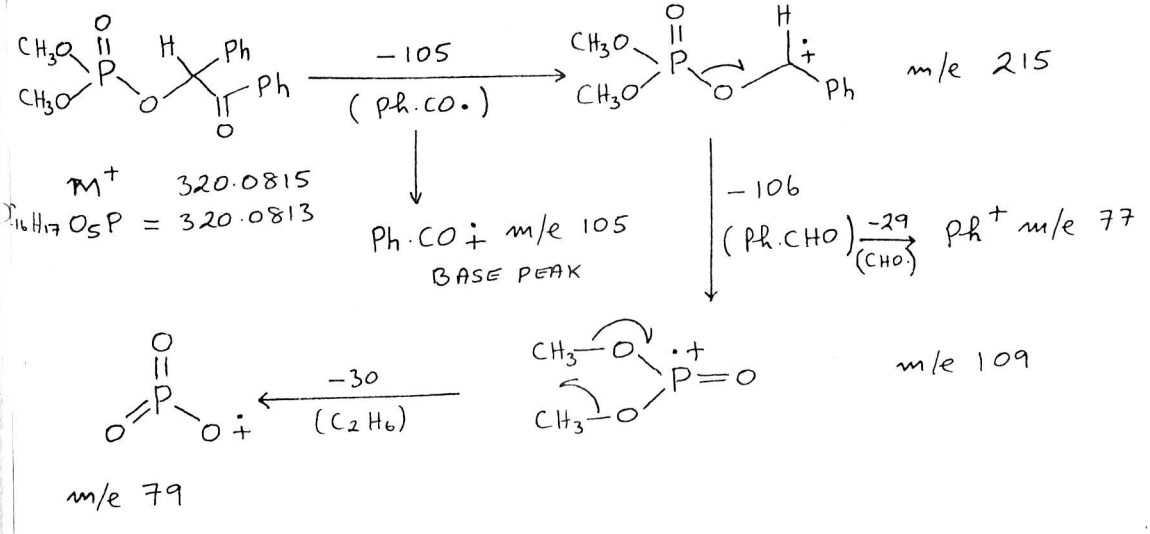
A. Chloral: ethylene methyl phosphite adduct



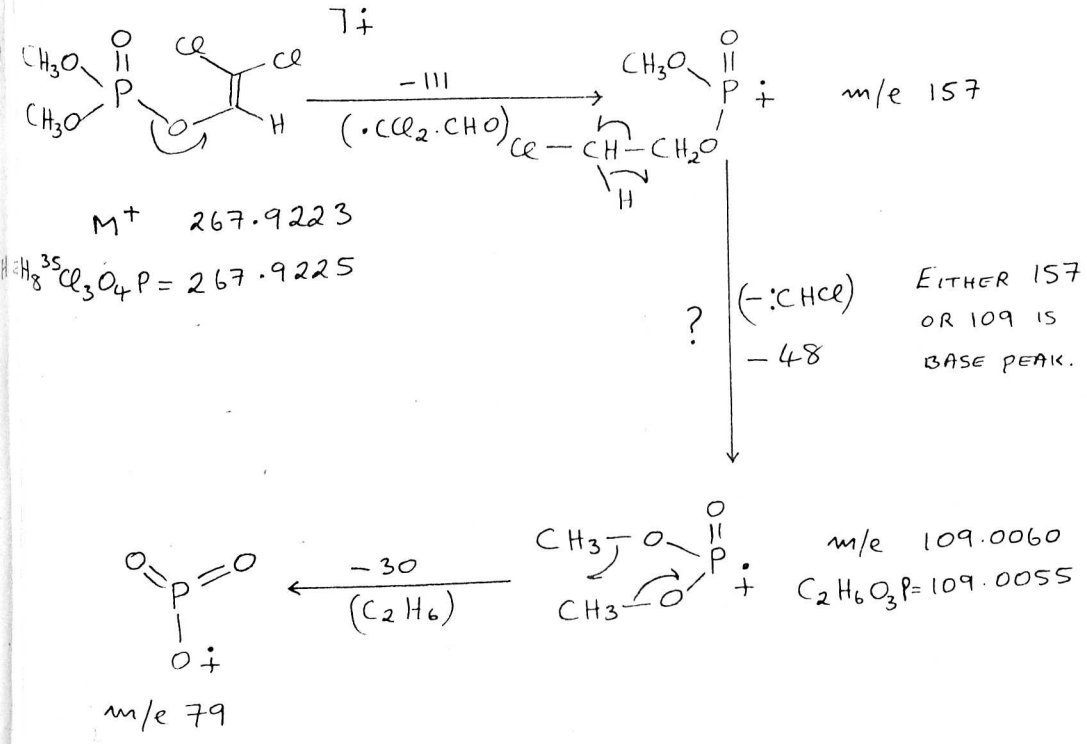
B. Chloral: methyl o-phenylene phosphite adduct



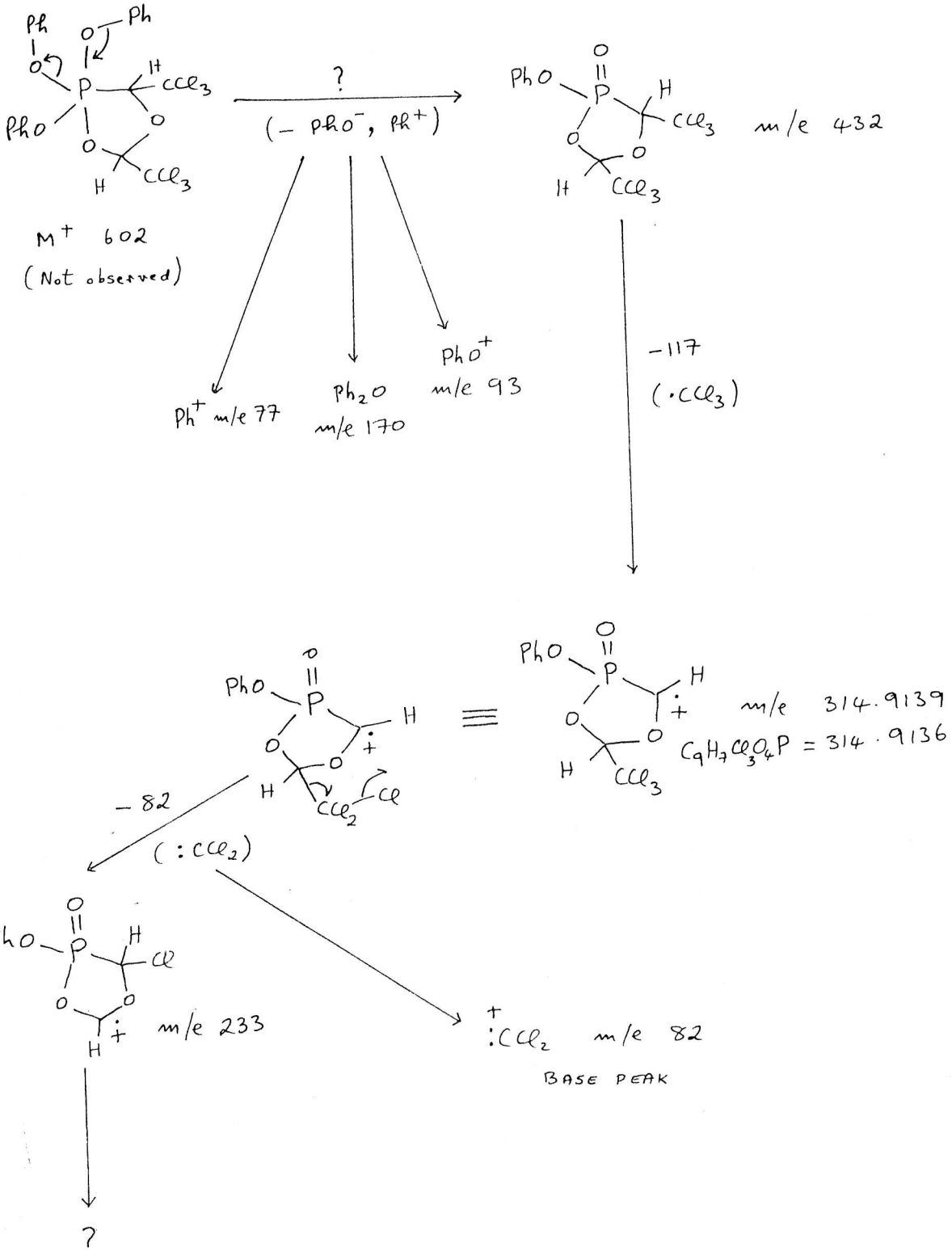
C. Dimethyl 1-benzoyl benzyl phosphate



D. 2-chloroethyl 2,2-dichlorovinyl methyl phosphate



E. Triphenyl phosphite: chloral adduct



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